CLINICAL TRIAL PROTOCOL AND STATISTICAL ANALYSIS PLAN

IIR 15-359 / NCT03860818

Improving Transplant Medication Safety through a TEchnology and Pharmacist Intervention (ISTEP)

Last updated August 11, 2021

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PRÉCIS

Study Title

Improving Tra**N**splant Medication **S**afety through a **TE**chnology and **P**harmacist Intervention **(ISTEP)**

Objectives

Primary

1. 24-month rate of hospitalization and emergency room visits compared between the intervention and usual care groups

Secondary

2. 24-month total estimated health care costs, compared between the intervention and usual care groups
3. Estimated graft survival rates, compared between the intervention and usual care groups and defined as the proportion of patients that continue to have a functioning allograft at the end of the 24-month study
4. Estimated patient survival rates, compared between the intervention and usual care groups and defined as the proportion of patients alive at the end of the 24-month study
5. Potential medication safety issues, defined as the proportion of patients with the following, based on automated reports for the transplant medication dashboard:
    a. Percent of patients with missing labs
    b. Percent of patients alarming lab values without follow up scheduled
    c. Immunosuppression adherence, estimated using the proportion of days covered (PDC)
    d. Percent of patients on significant drug interaction without a immunosuppressant level
    e. Percent of patients with hospital discharge or ED visit without follow up scheduled
6. Proportion of alerts that were deemed clinical relevant and actionable by the intervention pharmacists
7. Proportion of interventions that were deemed to be accepted when made to other providers based on dashboard reporting information
8. Average time required to respond to each alert

Design and Outcomes

This is a 24-month, prospective, multicenter, cluster-randomized, parallel-arm, controlled clinical trial assessing the impact of a pharmacist-led technology-enabled intervention designed to improve immunosuppression medication safety

in veteran organ transplant recipients. The study includes 10 sites, five sites randomized to standard clinical care and five to standard care plus the technology-enabled pharmacist intervention.

Study efficacy will be determined by comparing the rates of hospitalizations and ER visits between intervention and control study site veteran organ transplant recipients, while adjusting for baseline patient, provider and facility characteristics. Secondary measures include comparing estimated healthcare costs and determining dashboard functionality, dashboard actionability and pharmacist intervention types and acceptance rates. We will also assess the overall incidence and severity of drug-related problems and graft and patient survival rates and compare these between the intervention and control sites.

Interventions and Duration

The study will randomize 10 sites to usual care or usual care plus intervention in a parallel arm design and study duration will be 24-months.

The intervention will include a pharmacist that utilized a dashboard system to identify veteran organ transplant recipients with the potential of immunosuppressant medication-safety issues. The technology component of this intervention consists of the use of a dashboard system that performs population-level surveillance of organ transplant recipients and identifies those with potential drug-related problems, including non-adherence to immunosuppression medications, drug interactions, missing and worrisome trends in labs and recent hospitalizations and ED visits; then providing a real-time alert to the pharmacist, who will determine its relevance and intervene in an appropriate protocol-guided manner.

Sample Size and Population

There will be 10 sites included in this study with an estimated average of 169 veterans per site, totaling 1,689 veterans across the entire study population, divided approximately equally between the intervention and usual care groups

The patient population will consist of veterans that received solid organ transplants (kidney, liver, pancreas, heart, or lung) and receive their immunosuppression medications through the VA system. Patients will be identified using ICD-9 or 10 codes and VA medication prescription information.

1 STUDY OBJECTIVES

1.1 Primary Objective

Hypothesis:

1. Veterans in the intervention group will have significantly lower rates of hospitalizations and emergency room visits, as compared to the control group, by the end of the 24-month study

Objective:

1. Through a 24-month prospective, parallel arm, cluster-randomized, controlled multicenter study, measure the effectiveness of a pharmacist-led, technology-enabled intervention on reducing the rate of hospitalizations and emergency room visits in Veteran organ transplant recipients, as compared to usual care

1.2 Secondary Objectives

Hypotheses:

1. Veterans in the intervention group will have significantly reduced health care costs, as compared to the control group, by the end of the 24-month study
2. The immunosuppressant dashboard system will provide near real-time, actionable alerts that will allow the pharmacist to conduct timely intervenes on potential or ongoing drug-related problems

Objectives:

1. 24-month estimated health care costs, compared between the intervention and usual care groups
2. Estimated graft survival rates, compared between the intervention and usual care groups
3. Estimated patient survival rates, compared between the intervention and usual care groups
4. Potential medication safety issues, defined as the proportion of patients with the following, based on automated reports for the transplant medication dashboard:
    a. Percent of patients with missing labs
    b. Percent of patients alarming lab values without follow up scheduled
    c. Immunosuppression adherence, estimated using the proportion of days covered (PDC)

d. Percent of patients on significant drug interaction without a immunosuppressant level
e. Percent of patients with hospital discharge or ED visit without follow up scheduled

5. Proportion of alerts that were deemed clinically relevant and actionable by the intervention pharmacists
6. Proportion of interventions that were deemed to be accepted when made to other providers based on dashboard reporting information
7. Average time required to respond to each alert

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Within organ transplant, despite dramatic improvements in acute rejection rates, long-term graft survival has not improved to nearly the same degree. In kidney transplant, since 2003, there has been a 50% reduction in acute rejection rates; yet, during this same period of time, the allograft half-life has only increased by a modest 0.6 years.[6,7] 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%.[4] Drug-related problems, which encompass medication errors, non-adherence and adverse drug events, are a predominant cause of deleterious clinical outcomes in kidney transplant recipients; most notably, graft loss.[22] Our previous research, as well as studies from other groups, has demonstrated that approximately two-thirds of transplant recipients will experience at least one medication error.[11-13] Of more concern, nearly one in eight kidney transplant recipients experience a medication error which directly contributes to hospitalization and doubles the risk of graft loss. These medication errors are usually the result of unintentional non-adherence: patients have difficulty obtaining medications, gets confused from the fragmented care they receive or forget to take medications in a timely manner.[14] Non-adherence 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 landmark study by Sellares et al, 315 kidney transplant recipients were followed for roughly three years post-transplant; 47% of the 50 allografts that failed during this time were due to AMR; 32% of patients were identified as non-adherent and one-half of all AMRs were due to this. Remarkably, medication non-adherence was 10 times more frequent in patients with graft failure (32% vs. 3%, $p<0.001$).[22] As most medication non-adherence is unintentional, with the proper monitoring and follow-up, this devastating risk factor is modifiable. Other drug-related problems, beyond non-adherence, also significantly contribute to deleterious post-transplant events. A study by Friedman et al demonstrated that of 149 medication errors identified in 93 ambulatory organ transplant recipients, 44% were due to iatrogenic causes, including 13% from a prescribing error and 13% from a dispensing error. Importantly, 26% of these errors led to clinical significant events, including

laboratory abnormalities (8%), physical issues (5%), hospital admission (8%) and an outpatient intervention (8%). Thus, to improve medication safety, interventions should not only focus on the patient, but also engage the health care providers.[11]

Although immunosuppression is effective at preventing rejection, adverse drug events are nearly universal and associated with significant morbidity. Several studies suggest that adverse drug events, particularly infection from over-immunosuppression and calcineurin inhibitor nephrotoxicity, may be a predominant cause for the discordance between reductions in acute rejection and lack of improvements in graft survival. Parasuraman et al demonstrated that infectious etiologies have surpassed rejections as the leading cause of graft loss.[9] Our previous research demonstrates that immunosuppressant adverse drug events are associated 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).[14] In other comorbidities, adverse drug events have clearly been established as a major risk factor for medication non-adherence.[23-26] Therefore, early recognition of adverse drug events in transplant recipients will likely help prevent downstream clinical sequelae, including non-adherence and irreversible immunosuppressant toxicities. Research demonstrates that clinical pharmacists have the unique education and training to both identify these events early, while also developing strategies to mitigate or resolve the associated sequelae.[16,17,27-31]

Also of concern with the use of chronic immunosuppression therapy in the ambulatory care setting are drug interactions. The calcineurin inhibitors and mTOR inhibitors, which are widely utilized immunosuppressants, are metabolized through the cytochrome P450 3A4/5 enzyme system, making them prone to interactions. Due to their effects on the renal and nervous system, these drugs are also frequently associated with pharmacodynamic drug interactions and drug-disease interactions. This includes interactions with classes of medications that are the most frequently prescribed in the outpatient setting, such as NSAIDs and ACE inhibitors. These interactions can result in an acute and dramatic reduction in renal function and electrolyte disturbances, particularly hyperkalemia.[32,33] The impact of drug-related problems leading to graft 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%), as compared to those with a functioning transplant (2.8%).[34] A well-functioning kidney transplant has also been shown to dramatically reduce the progression of cardiovascular disease and associated events.[35-37] In other organ types, graft loss universally leads to either retransplant or death. In terms of cost, transplantation is highly cost-effective. However, due to high and varied peri-operative costs associated with this surgery, the break-even point can range from two to 11 years after transplant.[38,39] Once a kidney transplant fails, patients return to dialysis and costs to provide care accrue at a significantly higher rate.[40,41] 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.[14] These data, taken in its entirety, establishes the need for innovative interventions designed to improve medication safety and reduce drug-related problems in transplant recipients, by decreasing medication errors, non-adherence and adverse drug events;[10] Such medication safety improvements are needed to demonstrate significant progression in

the optimization of long-term graft outcomes and patient survival.

2.2 Study Rationale

Previous research provides evidence that this clinical trial is grounded on a strong conceptual model explaining the etiologies of medication safety events in transplant patients and supported by empirical evidence demonstrating the use of technology and pharmacist-led interventions can improve outcomes in transplant patients. The specific rationale for this study are based on the following:

Medication Safety Issues in Transplantation:

- Medication safety events are common in transplant recipients. In an analysis we conducted of 200 prospectively monitored transplant recipients, significant medication errors occurred in 64% of patients, with immunosuppressants associated with the error 48% of the time. Patient-related issues (taking the wrong dose prescribed or missing doses) caused 68% of these errors, with provider and systems issues accounting for the remaining third. Significant adverse drug events, defined as the Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, occurred a total of 327 times and within 87% of the study cohort. Patients that experienced a significant medication error contributing to a hospitalization developed more adverse drug events (2.1±1.0 vs. 1.6±1.1, p=0.030).[14]
- Previous research has demonstrated that transplant recipients numerous risk factors for the development of medication safety events, including: taking >10 medications concomitantly with more than 30 doses ingested per day, being prescribed narrow therapeutic index medications that are prone to drug interactions, taking chronic immunosuppressants with known debilitating side effects and having frequent dosage adjustments that occur during distantly, over the phone, during chart reviews. Additionally, long-term ambulatory transplant recipients usually receive care across multiple health care organizations; thus fragmented care, omissions, duplications and discrepancies in medication regimens are common within these patients. We have also established this as a major issue facing Veteran transplant recipients.[3,10-13]

Pharmacist-Led Interventions to Improve Medication Safety in Transplantation:

- Previous studies demonstrate that interdisciplinary quality improvement endeavors, which include the empowerment of pharmacists to implement initiatives aimed at improving medication use, can substantially improve medication safety in transplant recipients during the perioperative phase. This data demonstrated a 40% reduction in adverse drug events leading to hospitalization, 14% reduction in length of stay >3 days and 50% reduction in 14-day readmissions. Our follow-up study, which measured the impact of a pharmacist-led formal medication reconciliation initiative, demonstrated that, on average, 2.3 medication errors per

transplant recipient discharge were prevented (3.4 vs. 1.1, p<0.001, respectively); although, medication errors were still apparent in a significant number of discharges, establishing the need of pharmacist involvement in the ambulatory phase of care for these high-risk patients.[16,17]

Medication Safety in Veteran Transplants:

- Veteran transplant recipients are embedded within highly complex inter-facility systems of care, such that medication safety monitoring and care coordination in the ambulatory care setting is often fragmented and suboptimal. Our previous research has demonstrated that nearly two-thirds of Veteran transplant recipients are dual-users; with 62% having multiple providers managing the same conditions. This leads to a significant number of duplications and omissions in care. Medication discrepancies between systems are nearly universal as well. Thus, provider and system-level issues represent substantial reinforcing and enabling factors driving medication safety events in Veteran transplant recipients.[3]
- We completed an interrupted time series analysis, demonstrating significantly improved adherence to appropriate immunosuppression laboratory monitoring by using a population surveillance dashboard to identify Veteran transplant recipients with missing laboratory data, allowing the pharmacist to efficiently intervene by engaging the Veterans to either schedule labs or document non-VA care. Using segmented regression, we demonstrated a 38% improvement in monitoring (p<0.001), at a rate of 4.7% improvement per month for the first six months of the intervention (p<0.001).[18] Thus, we have strong preliminary data that the dashboard is functional and can be an effective instrument to identify Veterans needing attention in a time-sensitive and efficient manner. This dashboard system is currently being utilized at multiple sites (one in VISN 7 and several in VISN 12). For this proposal, we plan to expand the dashboards functionality and incorporate its use by pharmacists as part of clinical care at the 5 sites randomized to the intervention arm of this study.

The cluster-randomized design of this study was chosen for a number of important reasons. First, this study design will allow investigators to test a promising intervention against a similar control group with respect to patient constitution and time. The use of randomization at the site level will allow us to complete the 24-month study within a reasonable period and within the budget constraints. Using the cluster randomized parallel design at 10 sites will provide sufficient patient numbers to meet statistical power to detect clinically meaningful differences in health care utilization. Randomization at the patient-level, as opposed to the site, would not be feasible, as there would be a high probability of cross-contamination based on the intervention proposed and the technology component, which uses site-specific population surveillance. Additionally, randomization at the patient-level would substantially prolong enrollment, thus making completion within 4 years infeasible. Other trial designs were considered and discussed with the investigational group, including stepped-wedge, interrupted time series, one group pre-post test, one group post-test only and a

traditional patient-level randomization. The stepped wedge is the best alternative to our proposed study but would provide limited time to evaluate outcomes at some of the sites. Given the proposed intervention type, the use of population-surveillance technology, the number of sites recruited and the time and budget constraints, the investigative team felt that the parallel-group, cluster randomized controlled trial was the strongest in terms of methodology, internal validity, statistical power, feasibility and likelihood of success.

3 STUDY DESIGN

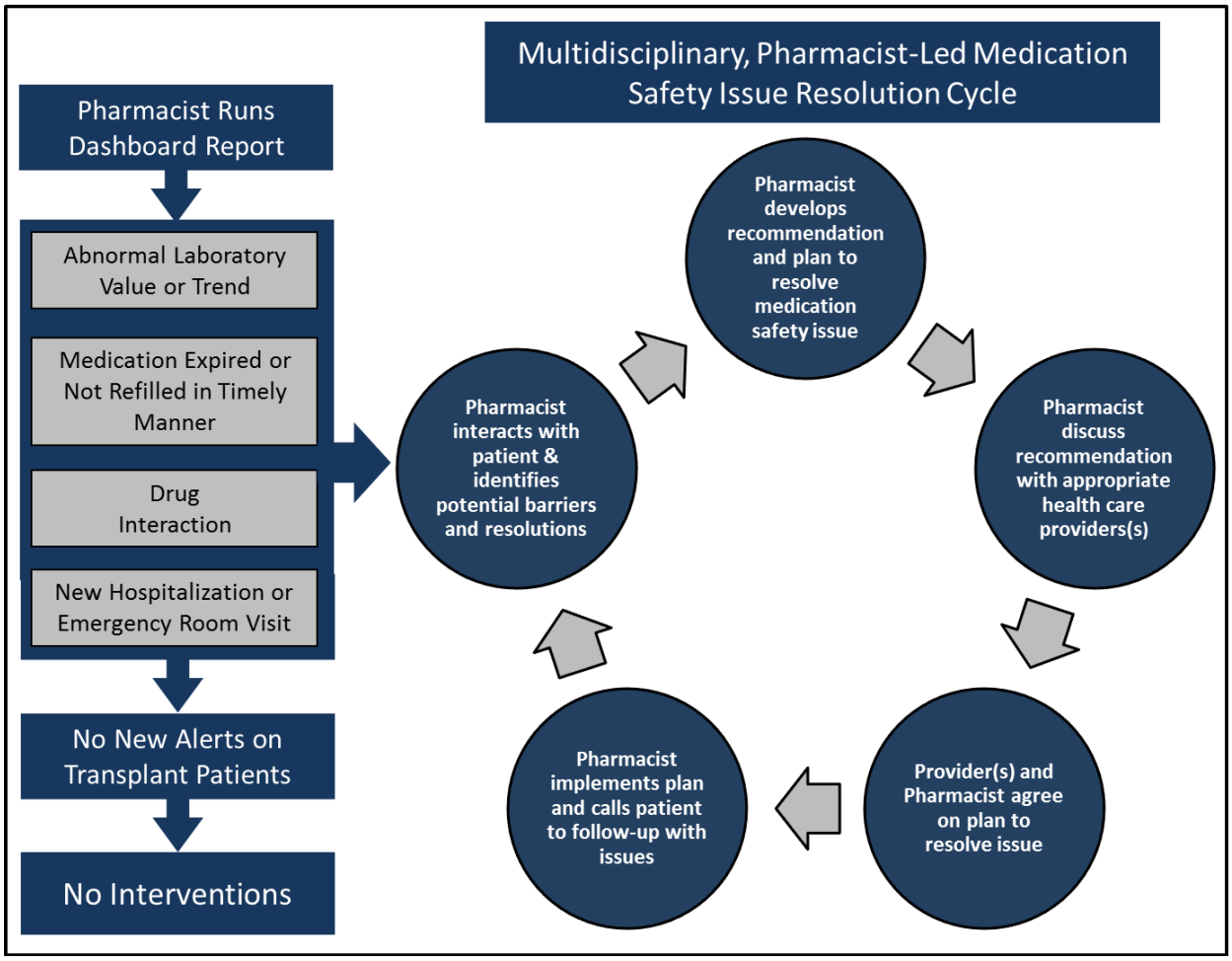
This is a 24-month prospective, parallel arm, cluster-randomized, controlled multicenter study in veteran organ transplant recipients receiving immunosuppressant medications through the VA system. The trial will randomize 10 VA sites, 5 to standard of care and 5 to standard of care plus the intervention. The intervention consists of a pharmacist-led health services endeavor utilizing a transplant medication dashboard system that monitors and reports on potential immunosuppression-related safety issues. The study will use prospective methodology to monitor patients for 24-months following site-randomization, comparing outcomes between the intervention and control sites. Clinical outcomes that will be assessed include health care encounters (hospitalizations and ER visits), estimated health care costs, and graft and patient survival. The functionality of the dashboard system will also be assessed by analyzing the proportion of actionable alerts created by the system as well as the proportion of missing labs, proportion of alarming lab values without follow up scheduled, estimated immunosuppression adherence (using the proportion of days covered [PDC]), proportion of significant drug interactions without an immunosuppressant level and the proportion of hospital and ER visits without follow up.

The study population will consist of veteran organ transplant recipients that receive immunosuppressant medications through the VA system. Organ transplant recipients will be identified using ICD-9/10 codes from the VA electronic health record. Once identified, active medications will be queried and those receiving immunosuppressant medications to prevent rejection (tacrolimus, cyclosporine, azathioprine, mycophenolate, sirolimus, everolimus, or belatacept) will be included in the study.

The study will take place at 10 VA sites, with 5 being randomized 5 to standard of care and 5 to standard of care plus the intervention. The 10 site locations are listed in the participating sites section of this protocol. After randomization and site initiation, all intervention sites will go live on the dashboard and pharmacist-led intervention simultaneously. Following this, patients at both the intervention and standard of care sites will be prospectively monitored for 24 months, in a parallel fashion.

The sites randomized to the intervention arm will continue to use current standard of care procedures within their sites, while also utilizing the dashboard system daily to identify veteran transplant recipients with potential medication safety issues. Each day, the pharmacists will open the dashboard system, which is updated at approximately 7:00 AM each morning. The system will identify new patient-specific alerts that will inform the pharmacist on potential medication safety issues. The pharmacist will then serve as a patient navigator, intervening to resolve the medication safety issue, by using

detailed protocols within the standard operating procedure (SOP) manual that the pharmacists will be trained on prior to study initiation. Once the pharmacist validates that the dashboard alert is a relevant issue, they will develop a management plan using these protocols (Figure above), discuss the recommendations with the providers (when necessary), agree on a plan, and implement the plan. The primary medication safety issues the intervention pharmacists will be alerted to, and address are laboratory abnormalities, medication non-adherence, drug interactions and medication



coordination/communication issues. For laboratory abnormalities, common issues encountered within transplant patients include electrolyte irregularities, organ dysfunction, drug level outliers and cytopenias. For each of the laboratory values that will be monitored and reported in the dashboard, a detailed algorithm in the standard operating procedures (SOP) manual delineating how to address the issues will be used for the pharmacist-led intervention. For instance, it is well known that magnesium levels are low in transplant recipients due to a side effect of calcineurin inhibitors.[50] Strategies to address this include dietary interventions and supplementation. Issues with out-of-range drug levels will also be addressed. These include ensuring the patient is taking the correct dose, ensuring the level is a true trough value, checking for new drug interactions and adjusting the dose when necessary. When medication non-adherence is identified as a potential issue, the pharmacist will determine if it is deliberate or unintentional. Strategies to address deliberate non-adherence include removing

perceived or actual barriers, using motivational interviewing, and addressing side effects and cost issues. For unintentional non-adherence, pharmacists can implement trigger reminder strategies, simplify regimens, and re-educate. Within drug-interaction alerts, the intervention will focus on reducing the impact of these through changing of regimens (when appropriate), educating patients and/or providers and increased monitoring and surveillance.[51] Alerts for medication coordination issues will encompass discharges from the ER and hospital and missed laboratory assessments. The intervention pharmacist will ensure accurate and safe medication regimens through medication reconciliation and improved medication safety surveillance through the scheduling and follow up of laboratory assessments.[17] To ensure fidelity across sites and efficiency for providers, the specific day-to-day tasks involved with this intervention, which include assessing and intervening on the alerts and appropriate follow up with patient and providers, will be delivered using the SOP manual.[15-17]

4 SELECTION AND ENROLLMENT OF STUDY SITES AND PATIENTS

Patients will be included in this study if they are veteran organ transplant recipients that receive immunosuppressant medications through the VA system. Organ transplant recipients will be identified using ICD-9/10 codes from the VA electronic health record (CPRS), with this data housed in the CDW. Once identified, active medications will be queried and those receiving immunosuppressant medications to prevent rejection (tacrolimus, cyclosporine, azathioprine, mycophenolate, sirolimus, everolimus, or belatacept) will be included in the study. There are no exclusion criteria for patients in this study as recruitment is at the VA site-level. As this is a cluster-randomized study and randomization will occur at the site level and not the patient-level, participants will not be recruited for the study, and data collection will occur through querying and linking the VA CDW, the SRTR transplant registry and CMS data repositories. We will request waiver of written documentation of patient informed consent. We will also request HIPAA authorization waiver as well for all patients. The following protected health information (PHI) elements will be required to complete the study with the HIPAA authorization waiver.

PHI Required for Study	**Rationale**
Social Security Number	Require real SSNs to create finder file and send to Scientific Registry of Transplant Recipients (SRTR) to acquire baseline transplant information and graft outcomes
Date of transplant, date of clinical events (including graft loss, rejections,	Require dates to ensure events occurred during the study period and to conduct

hospitalizations, emergency department visits and death)	time to event survival analyses for primary and secondary aims
Zip codes	Require zip code to assess and adjust for potential geographic confounding in multivariable analyses

4.1 Inclusion Criteria (require both to be included)

- Veteran organ transplant recipients will be identified using ICD-9/10 codes from the VA electronic health record (CPRS). Patients must have an active code stating they are a recipient of an organ transplant. The following codes will be utilized:
    - ICD-9 codes: V42.0, V42.1, V42.6, V42.7, V42.83, V42.84, 996.81, 996.82, 996.83, 996.84, 996.86, 52.80

OR

    - ICD-10 codes: C80.2, T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, T86.2, T86.20, T86.21, T86.22, T86.23, T86.290, T86.298, T86.3, T86.30, T86.31, T86.32, T86.33, T86.39, T86.4, T86.40, T86.41, T86.42, T86.43, T86.49, T86.810, T86.811, T86.812, T86.818, T86.819, T86.9, Z48.2, Z48.21, Z48.22, Z48.23, Z48.24, Z48.280, Z48.288, Z48.298, Z94.0, Z94.1, Z94.2, Z94.3, Z94.4, Z94.83

AND

- Actively receiving at least one anti-rejection medication dispensed by the VA site. These medications include tacrolimus, cyclosporine, azathioprine, mycophenolate, sirolimus, everolimus, and belatacept.

4.2 Exclusion Criteria

- There are no exclusion criteria for patients in this study as recruitment is at the level of the VA site.
- All veterans meeting inclusion criteria will be monitored by the dashboard system and will be included in the outcomes assessment. Patients may enter or exit the study in a rolling manner, which will be accounted for during analyses.

4.3 Study Enrollment Procedures

Once IRB approval is obtained (via central IRB), each potential participating pharmacist will undergo informed written consent. Following this, each site will be randomized to

standard care or standard care plus the pharmacist-led intervention. To ensure a roughly equal number of patients between the two comparison groups, randomization will be stratified by estimates veteran organ transplant recipients (<125 versus ≥125 active patients). After randomization, each participating pharmacist will be informed of their assigned group. Those in the intervention arm will be trained on the dashboard system, utilizing the dashboard, and delivering the intervention. Those in the usual care group will continue to provide the same level of care they are currently providing as part of their normal day-to-day activities and job functions.

If a site or participating pharmacist withdraws prior to study initiation, if possible, it will be replaced with a suitable alternative site/pharmacist. If a site pharmacist withdraws after initiation, the investigational team will determine if the site needs to be replaced. This will depend on how far along the intervention is and the number of veterans impacted by the withdrawal.

Because this is a cluster-randomized trial, and randomization occurs at the site level, we will not recruit, consent, or enroll at the subject level. We will request waiver of written documentation of patient informed consent. We request waiver of HIPAA for all patients.

5 STUDY INTERVENTIONS

5.1 Interventions

The sites randomized to the intervention arm will continue to use current standard of care procedures within their sites (described below), while also utilizing the dashboard system daily to identify Veteran transplant recipients with potential medication safety issues. Each day, the pharmacists will open the dashboard system, which is updated each morning. The system will identify new patient-specific alerts that will inform the pharmacist on potential medication safety issues. The pharmacist will then serve as a patient navigator, intervening to resolve the medication safety issue, by using protocols embedded within the SOP manual that the pharmacists will be trained on prior to study initiation. Once the pharmacist validates that the dashboard alert is a relevant issue, they will develop a management plan using these protocols, discuss the recommendations with the providers (when necessary), agree on a plan, and implement the plan.

The four primary medication safety issues the intervention pharmacists will be alerted to and address are laboratory abnormalities, medication non-adherence, drug interactions and medication coordination/communication issues. For laboratory abnormalities, common issues encountered within transplant patients include electrolyte irregularities, organ dysfunction, drug level outliers and cytopenias. For each of the laboratory values that will be monitored and reported in the dashboard, a detailed algorithm will be provided delineating how to address the issue, within the SOP manual (see below). As one example, it is well known that magnesium levels are low in transplant recipients due to a side effect of calcineurin inhibitors.[50] Strategies to address this include dietary interventions and supplementation. Issues with out-of-range drug levels will also be

addressed. These include ensuring the patient is taking the correct dose, ensuring the level is a true trough value, checking for new drug interactions and adjusting the dose when necessary. When medication non-adherence is identified as a potential issue, the pharmacist will determine if it is deliberate or unintentional. Strategies to address deliberate non-adherence include removing perceived or actual barriers, using motivational interviewing, and addressing side effects and cost issues. For unintentional non-adherence, pharmacists can implement trigger reminder strategies, simplify regimens, and re-educate. Within drug-interaction alerts, the intervention will focus on reducing the impact of these through changing of regimens (when appropriate), educating patients and/or providers and increased monitoring and surveillance.[51] Alerts for medication coordination issues will encompass discharges from the ER and hospital and missed laboratory assessments. The intervention pharmacist will ensure accurate and safe medication regimens through medication reconciliation and improved medication safety surveillance through the scheduling and follow up of laboratory assessments.[17]

To ensure fidelity across sites and efficiency for providers, the specific day-to-day tasks involved with this intervention, which include assessing and intervening on the alerts and appropriate follow up with patient and providers, are fully developed and incorporated within the SOP manual. This manual was vetted by transplant clinicians, provided to each intervention site pharmacist, with appropriate training.

Monitoring Variable	Absolute Value Thresholds	Trajectory Threshold
Laboratory Assessments – ONLY OUTPATIENT		
Potassium (K)	<3 or >5.5 mEq/L	>30% Change
Bicarbonate (CO2)	<18 or >30 mEq/L	>30% Change
Blood Urea Nitrogen (BUN)	>40 mg/dL	>30% Increase
Creatinine (Cr)	>2.5 mg/dL	>20% Change
Glucose (Gluc)	<60 or >300 mg/dL	>30% Change
Calcium (Ca)	<7 or >10 mg/dL	>30% Change
Magnesium (Mg)	<1.0 or >2.5 mEq/L	>30% Change
Phosphorus (PO4)	<2.0 or >5.0 mg/dL	>30% Change
White Blood Cell (WBC) Count)	<3.0 or >15.0 cells/mm3	>30% Change
Hemoglobin (Hgb)	<8 or >15 gm/dL	>20% Change
Platelets (Plt)	<50 or >500 cells/mm3	>30% Change
Alanine Aminotransferase (ALT)	>160 U/L	>30% Increase
Total Bilirubin (T Bili)	>1.5 mg/dL	>20% Increase
Hemoglobin A1C	>8%	>20% Increase
Low Density Lipoprotein (LDL)	>190 mg/dL	>30% Increase
Triglycerides (TG)	>500 mg/dL	>30% Increase
Tacrolimus (FK) Trough	<3 or >15 ng/mL	>20% Change
Cyclosporine (CyA) Trough	<30 or >400 ng/mL	>20% Change
Sirolimus (Rapa) Trough	<2 or >8 ng/mL	>20% Change
Everolimus (RAD) Trough	<2 or >8 ng/mL	>20% Change
Interacting Drugs	**Trigger Definitions**	
Enzyme Inhibitors – INPATIENT OR OUTPATIENT		
Macrolides (clarithromycin, erythromycin, telithromycin)	Initiation Discontinuation Dose Change >20%	
Azoles (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, isavuconazole)		
Calcium Channel Blockers (diltiazem, verapamil)		
HIV (nafazodone, delaviridine, saquinavir, nelfinavir, indinavir, amprenavir)		
Miscellaneous (boceprevir, telaprevir, cimetidine, chloramphenicol, danazol)		
Enzyme Inducers - INPATIENT OR OUTPATIENT		
Antiepileptics (carbamazepine, phenytoin, phenobarbital)	Initiation Discontinuation Dose Change >20%	
Rifamycins (rifampin, rifabutin)		
Miscellanious (St. John's Wort, neviripine, efavirenz, enzalutamide)		
Other		
atorvastatin >10mg, rosuvastatin >10 mg, simvastatin >10 mg with Cyclosporine ONLY	Initiation Discontinuation Dose Change >20%	
Encounters	**Trigger Definition**	
Hospitalization or ED visit	At discharge	
Immunosuppression	**Trigger Definition**	
Tacrolimus, cyclosporine, mycophenolate, azathioprine, sirolimus, everolimus, prednisone	PDC <80%, late refill (10 days), drug expired	

5.2 Training for Study Interventions

Prior to the initiation of the study, the pharmacists randomized to the intervention will participate in a two-day training conference held at the coordinating site. During this training, the dashboards functionality will be reviewed, along with the SOP manual which fully guides interventions. During this training conference, the intervention pharmacists will also participate in case-based competencies.

Sessions that occur during this conference include:

1. General overview of organ transplantation
2. Review of immunosuppression pharmacology and pharmacokinetics
3. Review of transplant immunosuppression dashboard specifics
4. Running reports to create alerts
5. Assessing clinical relevance of alerts
6. Alert categories
7. Interventions to address alerts
8. Suppressing alerts
9. Clinical and research documentation
10. Motivational interviewing techniques – face-to-face and over the phone
11. Provider collaboration strategies
12. Case-reviews

The investigational team and outside consultant experts will lead these sessions. We will also utilize expertise from the local VA and transplant center to conduct training sessions when needed. In addition, during the 24-month intervention period, we will have monthly teleconferences with the intervention pharmacists at the five sites to discuss and address issues with the dashboard and/or intervention. As an additional safety measure and to further ensure intervention fidelity, we will have experts available to discuss patient issues with sites participating in the intervention. These include the PI, transplant nephrology, transplant hepatology and an internal medicine physician. All interventions will be documented in the medical record using an approved note template. As another quality assurance step, through querying the notes entered into CPRS by intervention site pharmacists, we will capture specific interventions made by the study site pharmacists; these will be monitored by the PI and investigational team to ensure clinical appropriateness. If there are concerns with specific interventions made by study site pharmacists, these will be addressed on a case-by-case basis. During the course of the study, if an intervention pharmacist has a particular issue that is time sensitive and is unsure how to address it, they will have the ability to call and/or page the PI or investigational team, which includes expertise in transplant-related care. For non-urgent issues, pharmacists can send secure emails to investigational team members or bring up the issue during conference calls. Thus, there will be ample training and resources available to all intervention site pharmacists to ensure the study is conducted in a safe clinically appropriate manner with strong fidelity.

5.3 Usual Care

Both the control and intervention groups will continue to receive usual care as part of this study. Patients at the control sites will receive standard of care, and patients at the intervention sites will receive standard of care plus the pharmacist-led intervention. Usual care for Veteran organ transplant recipients across the 10 study sites varies somewhat, but generally includes the following: at most sites, nurse coordinators and/or mid-level practitioners are responsible for general transplant patient oversight, including ensuring laboratory assessments are scheduled/reviewed and medication regimens are accurate and up to date. However, large patient numbers and workload constraints preclude these health care professionals from prospective detailed daily monitoring of patients. If there is non-adherence to laboratory assessments or medications, they are rarely identified concurrently or early after they occur. Thus, medication safety issues that arise usually do not get identified or addressed until they have caused a clinically significant issue, leading to a health care encounter (clinic visit, ER visit, hospitalization). In addition, during this long-term ambulatory phase of care for transplant patients, pharmacists usually act as consultants and are only involved in direct patient care if an issue arises, and the nurse or provider engages the pharmacist for assistance. Within usual follow up care, pharmacists do not conduct routine daily surveillance of all transplant patients. Most transplant patients have multiple physician providers, both within and outside the VA system, providing care and medication management. This includes a primary care physician to manage common comorbidities (hypertension, diabetes, etc.) and a specialist (nephrology, hepatology) to manage allograft function; other specialists, including endocrinologists and cardiologists, are commonly involved with this patient population as well. Thus, care coordination and communication across these providers and health care organizations can often be fragmented. This usual care environment is complex and difficult to navigate, even for patients with high health literacy.[3,18]

5.4 Adherence Assessment

To ensure fidelity across sites and efficiency for intervention providers, the specific day-to-day tasks involved with this intervention, which include running the dashboard, assessing and intervening on the alerts and appropriate follow up with patient and providers, are fully developed in the SOP manual. This manual was vetted by transplant clinicians, provided to each intervention site pharmacist with appropriate training. In addition, we will have experts available to discuss patient issues with sites participating in the intervention. These include the PI, transplant nephrology, transplant hepatology and an internist.

To assess adherence to be SOP, all interventions will be documented in the medical record using approved note templates, including a specific transplant medication monitoring note which has already been developed and is in use by pharmacists in VISN 7 and VISN 12. Through querying the notes entered into CPRS by intervention

site pharmacists, we will capture specific interventions made by the study site pharmacists; these will be monitored by the PI and investigational team to ensure clinical appropriateness. This is particularly the case for interventions involving changes in immunosuppression regimens. If there are concerns with specific interventions made by study site pharmacists, these will be addressed on a case-by-case basis. During the course of the study, if an intervention pharmacist has a particular issue that is time sensitive and is unsure how to address it, they will have the ability to call and/or page the PI or investigational team, which includes expertise in transplant-related care. For non-urgent issues, pharmacists can send secure emails to investigational team members or bring up the issue during conference calls.

Adherence to the intervention and the SOP manual will be monitored by the coordinating study site. Specific interventions will be reviewed in a concurrent fashion. All deviations or issues that are identified will be reviewed by the study team and addressed. If a concerning pattern of non-adherence develops at a particular study site, the PI, in conjunction with the Co-Is and data safety monitoring team as the right to remove that site from the study. Replacement of a site will depend on criteria discussed in the study enrollment procedures section of this protocol.

6 STUDY PROCEDURES

Because of the nature of this intervention, all care that is provided, including laboratory and clinic visits, will be considered as usual care. The intervention consists of increased review of patients by a pharmacists and increased scrutiny of patients' medication regimens and laboratory values, through the use of a dashboard surveillance system. However, any interventions that are made as a result of this increased review will be considered usual care as they are directly related to monitoring of the organ transplant and immunosuppression medications. Thus, there are no study procedures that will occur above and beyond usual care procedures, which are described in the usual care section of this protocol.

The procedures unique to this study includes randomization of sites to use of the dashboard (intervention) or usual patient care review, training of the five intervention site pharmacists, site initiation and monitoring of intervention integrity and fidelity during the 24-month intervention phase of the study. No patient-specific procedures or interventions will occur that are above and beyond usual care will occur as part of this study.

7 SAFETY ASSESSMENTS

The impact of study interventions on patient outcomes will be closely monitored by an internal oversight committee (IOC). The IOC will consist of the PI, co-investigators, study coordinator, data manager and consultants on the proposal. The functions of the IOC will include: 1) providing scientific oversight; 2) reviewing all serious adverse 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 IOC will meet bi-annually and as necessary by telephone. The recommendations of the IOC will be reviewed and the PI will take appropriate corrective actions as needed. As part of this oversight, we will also recruit an independent transplant nephrologist that is not affiliated with this study to provide their expertise and review of all study activities. This expert will conduct the following:

1) Review the research protocol and plans for data and safety monitoring.
2) Evaluate the progress of the intervention, including periodic assessments of data quality and timeliness, site enrollment and retention, participant risk versus benefit, integrity of the intervention, and other factors that can affect study outcome.
3) Consider factors external to the study when interpreting the data, such as scientific or clinical developments that may impact the safety of study participants or the ethics of the study.
4) Make recommendations to the IOC, IRB, and VA R&D/VA HSR&D for continuation or termination of the study.
5) Protect the confidentiality of study data and monitoring.

The independent transplant nephrologist will have the authority to discontinue the trial temporarily or permanently if they perceive that harm is occurring due to the intervention. They will meet with the IOC to review serious adverse event reports, patient complaints if any, and site issues. Data will be provided at these meetings on key variables that may indicate harm, including, hospitalizations, ED visits, graft loss and death. The IOC biostatistician will evaluate the confidentiality and integrity of the database and the procedures for recording and storing confidential files. The independent transplant nephrologist will also review the elements of the plan to manage emergencies.

7.1 Serious Adverse Events (SAEs)

The intervention for this trial does not involve the administration of medications or investigational agents, but rather supplemental pharmacist-led care provided in addition to usual care already delivered to veteran organ transplant recipients. Thus, the intervention is considered minimal risk research. As part of this study, SAEs will be monitored, compared between the intervention and usual care group and reported to the IOC and independent transplant nephrologist on a bi-annual basis.

SAEs are defined as hospitalizations, ED visits, graft loss and death. Hospitalizations and ED visits will be obtained from VA CDW data housed in the VINCI environment. Graft loss events will be obtained from SRTR data linked to the VA data, while death will be obtained from both SRTR and VA CDW data. Due to the minimal risk of this study intervention and the fact that the intervention does not involve the administration of investigational agents, adverse events, including abnormalities in laboratory values, new syndromes or diseases or new or worsening patient symptoms will not be monitored or reported as a part of this study. These will be monitored and addressed under normal usual care provided to the veteran at the study sites.

7.2 Reporting Procedures

All reporting of safety concerns will occur through the IOC, as described above. The IOC will meet bi-annually and as necessary by telephone. The IOC will review reports created by the study biostatistician which incorporate clinical outcomes and SAEs, including rates of hospitalization, ED visits, graft loss and death, compared between the two groups. The recommendations of the IOC will be reviewed and the PI will take appropriate corrective actions as needed. As part of this oversight, we will also recruit an independent transplant nephrologist that is not affiliated with this study to provide their expertise and review of all study activities. This expert will conduct the following:

1) Review the research protocol and plans for data and safety monitoring.
2) Evaluate the progress of the intervention, including periodic assessments of data quality and timeliness, site enrollment and retention, participant risk versus benefit, integrity of the intervention, and other factors that can affect study outcome.
3) Consider factors external to the study when interpreting the data, such as scientific or clinical developments that may impact the safety of study participants or the ethics of the study.
4) Make recommendations to the internal IOC, IRB, and VA R&D/VA HSR&D for continuation or termination of the study.
5) Protect the confidentiality of study data and monitoring.

8 INTERVENTION DISCONTINUATION

The intervention will be discontinued based on the recommendations of the IOC and/or the expert transplant nephrologist opinion. These decisions will be based on bi-annual reports provided by the study biostatistician that will report SAE rates compared between the intervention and usual care groups. Discontinuation will be recommended if the intervention demonstrates increased harm or potential harm to veterans at sites randomized to the intervention. This decision will be made based on clinically or statistically significant differences that are apparent in SAE rates between intervention and usual care sites. Worrisome trends will also be considered in the IOC decision.

The study sample size and power analyses were not designed to specifically conduct interim analyses for outcomes and factor in early termination due to substantial improvements or futility. Thus, only safety concerns will be used as criteria for early stoppage.

If a particular site discontinues the intervention or usual care, attempts will be made to replace the site if possible. However, if the site discontinues the study after considerable intervention time has elapsed, data collection for follow up outcomes will be locked at that time point and a replacement site will not be recruited.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary hypothesis for the **ISTEP** study is that pharmacist-led immunosuppressant therapy management, facilitated through the use of innovative technology, will significantly improve immunosuppressant safety and clinical outcomes in Veteran transplant recipients.

The study will consist of a 24-month prospective, parallel arm, cluster-randomized, controlled multicenter study. The clinical trial will randomize 10 sites, 5 to standard of care and 5 to standard of care plus the below-discussed intervention, using prospective methodology to monitor patients for 24-months following site-randomization, comparing outcomes between the treatment and control sites. The cluster-randomized design of this study was chosen for a number of important reasons. First, this study design will allow investigators to test a promising intervention against a similar control group with respect to patient constitution and time. The use of randomization at the site level will allow us to complete the 24-month study within a reasonable period and within the budget constraints. Using the cluster randomized parallel design at 10 sites will provide sufficient patient numbers to meet statistical power to detect clinically meaningful differences in health care utilization. Randomization at the patient-level, as opposed to the site, would not be feasible, as there would be a high probability of cross-contamination based on the intervention proposed and the technology component, which uses site-specific population surveillance. Additionally, randomization at the patient-level would substantially prolong enrollment, thus making completion within 4 years infeasible. Other trial designs were considered and discussed with the investigational group, including stepped-wedge, interrupted time series, one group pre-post test, one group post-test only and a traditional patient-level randomization. The stepped wedge is the best alternative to our proposed study, but would provide limited time to evaluate outcomes at some of the sites. Given the proposed intervention type, the use of population-surveillance technology, the number of sites recruited and the time and budget constraints, the investigative team felt that the parallel-group, cluster randomized controlled trial was the strongest in terms of methodology, internal validity, statistical power, feasibility, and likelihood of success.

There are three main hypotheses this study aims to test:

1. Veterans in the intervention group will have significantly lower rates of hospitalizations and emergency room visits, as compared to the control group, at the end of the 24-month study.
2. Veterans in the intervention group will have significantly reduced health care costs, as compared to the control group, at the end of the 24-month study.
3. The immunosuppressant dashboard system will provide near real-time, actionable alerts that will allow the pharmacist to conduct timely intervenes on potential or ongoing drug-related problems.

9.2 Sample Size and Randomization

Based on the projected enrollment numbers, there is ample power to detect a statistically significant difference between the intervention and control groups with regards to the primary aim of hospitalization and ED visit rates. To determine this, we used data from a recent national study conducted between 2009-2012.[53] These results demonstrated that the rate of ED visits after transplant was 1.269 per person-year and 48% of those ED visits resulted in hospitalization. We will enroll 10 sites (5 sites for each study arm) and will have a total of just more than 1,600 patients that are roughly split between the intervention and control sites. We used a conservative estimate of an intra-cluster correlation of 0.05 and calculated a sample size of 1,350 to allow us to detect a 25% relative decrease in ED visit and hospitalization rates with 80% power. The 25% relative improvement in rates is a conservative estimate of intervention effect, based on previous pharmacist-led initiatives the investigators have conducted.[15,16] After allowing for 15% loss to follow up, we require a total of 1,600 to meet study power. We expect to have 1,689 patients based on site estimates. These power calculations were conducted using a two-sided test for counts with Poisson regression adjusting for intra-cluster correlation and with alpha set at 0.05.

9.2.1 Treatment Assignment Procedures

Randomization will occur at the site level (cluster randomized trial). Ten sites will be randomized to either the intervention arm or usual care arm using statistical software (SAS, SAS Institute, Cary, NC). Randomized will occur after all sites have agreed to participate and site-level regulatory approval has occurred. Randomization will be stratified by site using estimated sample size (<125 vs. ≥125 veteran organ transplant recipients). This will be done to ensure an approximate even distribution of patients across study arms.

9.3 Outcomes

The outcomes that are assessed for this proposal all relate to evaluating the impact of an intervention designed to improve medication safety within Veteran organ transplant recipients that receive immunosuppression through the VA system. This population represents a high-risk group that has a high incidence of medication errors, non-adherence and adverse drug events often leading to health care encounters, including ER visits and hospitalizations, which cause significant accrual of health care costs.

9.3.1 Primary outcome

The primary outcome for this study will include the overall rate of ER visits and hospitalizations, compared between the intervention and control groups. These encounters will be captured electronically throughout the 24-month study through the use of the CDW, stored in the VINCI environment. In addition, to ensure encounters are captured in a comprehensive manner, we will also link the VA CDW data to CMS (Medicare) claims data and capture non-VA ER and hospitalization encounters (after study completion). As most transplant patients are dual users and have Medicare

insurance benefits, this linkage will provide a more accurate assessment of these health care utilization.[3] We expect ER visits and hospitalizations to significantly decrease within the intervention arm, towards the latter half (second 12-months) of the study due to a lag effect of the intervention on this outcome. This expectation is based on our previous research in this field and assessment of pharmacist interventions on medication safety and reduced adverse drug events requiring hospitalization. ER visits and hospitalizations will be assessed and compared as described in the statistical analysis plan. These will be defined based on encounter criteria within the CDW and CMS data: all-cause ER visits and all-cause hospitalizations leading to at least one overnight stay will be included as events.

9.3.2 Secondary outcomes

Secondary assessment will include a cost benefit analysis. Overall health care costs accrued during the 24-month study, as well as those accrued in the 24-months prior to study initiation will be analyzed and compared between the control and intervention groups. Cost data will be standardized using the VA Health Economics Resource Center (HERC) definitions, which normalizes regional differences in costs due to variation in cost of living indices. As with the primary outcome, we will also acquire and link CMS claims data to gain a comprehensive assessment of costs, including those that accrue from non-VA care (after study completion). Costs will also be sub-analyzed into three predominant categories: inpatient costs, outpatient costs and pharmacy costs, as described in the statistical analysis plan. To fully assess if the intervention is has a direct monetary benefit, we will measure costs of the intervention will include estimates of time and resources to implement the dashboard and train and support the intervention site pharmacists. Similar to primary outcome, we expect that as ER visits and hospitalizations decrease within the intervention arm, there will be a corresponding decrease in overall costs as well, predominantly driven by inpatient costs. We expect this decrease to occur during the second 12 months of the study period, as the intervention is likely to have a lag effect on this outcome as well.

Another secondary outcome is to assess the success of the dashboard systems expansions and utilization. To do so, we will evaluate the dashboard's functionality by measuring and reporting descriptive statistics for the alert numbers, alert relevance, time and the actions taken with regards to the alert and the intervention magnitude. We will measure and report the time effort needed to conduct the interventions by study site pharmacists. Using REDCap, we will build an electronic data capture system, which allows the intervention pharmacists to efficiently enter alert and intervention information through a web-based portal, which will be housed within the VINCI environment. This information will be captured during the first 12 months of the intervention period, which will provide ample data without overwhelming the clinical pharmacists throughout the 24-month study. These measures will allow us to ascertain if the expanded dashboard is meeting expectations, with regards to functionality and efficiency. These measures will be assessed by investigators at quarterly intervals. If there is strong evidence to suggest particular components of the dashboard are not providing clinically relevant alerts or if the ratio of alerts to actionable alerts is exceedingly high, then the investigational team may decide to modify this component of the system. Thus, these

process measures will serve to both assess the dashboard functionality and allow for modification to improve the efficiency of the intervention. The time assessment data will allow us to determine the amount of time and effort implementing this system requires, as it relates to embedding it into normal workflow processes. This information will be important if the dashboard is deemed effective and is disseminated for use to across the VA, as it will allow administrators to accurately assess the required pharmacist time needed for implementation. Finally, we will assess the type and magnitude of the interventions made using this dashboard to ensure study fidelity. The categorization and magnitude of these interventions will be assessed using the Overhage criteria, which is a well-established and validated method used in numerous studies, included several published by the investigators proposing this study.[52] We will also assess the number of potential immunosuppression safety issues that occur and compare these between the two study arms. To do so, we will use the dashboard to provide monthly measurements of the following: percent of patients with missing laboratory assessments, percent of patients with alarming laboratory values without follow up scheduled, mean adherence to immunosuppression, based on refill timeliness and estimated using the PDC, percent of patients with a significant drug interaction without a immunosuppressant level and percent of patients with hospital discharge or ED visit without follow up scheduled. These will be measured in all patients and compared between the intervention and control groups at monthly intervals.

As an exploratory assessment, we will measure and compare graft survival and patient mortality between intervention and control sites. This study is not powered to determine if the intervention improves these clinical outcomes. However, it is well established that hospitalizations are a substantial risk factor for graft loss and patient death.[53] Thus, it is possible that this intervention may produce differences with regards to these clinical outcomes, even if the magnitude of the estimates does not produce statistically significant differences. We will also assess graft loss and mortality to ensure patient safety and that the intervention is not causing harm. These data elements (death and graft loss) will be captured through both the VA system (VINCI) and linking to the transplant registry (UNOS). The investigational team has experience with linking VA data to SRTR registry databases feels confident that this is feasible and will produce accurate measures of these important clinical outcomes.

9.4 Data Analyses

The data analysis will incorporate the intent-to-treat principle; namely, all participants enrolled in the intervention group will be included in the analysis and compared to all of the patients captured within the control group. If a patient dies, has graft loss or moves out of their study site, their data will be censored at that time point. For comparative statistical assessments within the utilization outcomes, the two groups will be compared using a generalized linear mixed models (GLMM) approach.[54] This approach allows for measurement of participants at different time points, clustering by study site, missing data under the assumption of missing at random (MAR), time varying or invariant covariates, and can also account for the effect of correlated longitudinal measurements within participants. In addition, GLMM accommodates a wide range of distributional assumptions such as dichotomous (e.g. binomial), count (e.g. Poisson), continuous

(e.g. Gaussian), and categorical or ordinal outcomes. For comparing the primary outcome (ED visit and hospitalization rates), we will use GLMM (with appropriate link function) with counts of these events as the outcome variable and intervention group (yes/no) as the primary independent variable. This analysis is equivalent to Poisson regression or negative binomial regression (in the case of over-dispersion), both special cases of GLMM. Additional adjustment covariables will be added to the model in a second set of analyses. Covariates will include patient sociodemographics: age, sex, race, comorbidities (using modified Elixhauser definitions), marital status and education. In these models, donor information (age, sex, race, deceased or living) and transplant characteristics (HLA mismatches, ischemic times, panel reactive antibody levels, time since transplant) will also be included. This will assist in making valid intervention effect estimates after accounting for baseline differences, as there may be patient-level differences between groups. The magnitude of between intervention differences on outcome variables (effect sizes) at each time point will be estimated using appropriate contrasts in the corresponding GLMM models.

We anticipate that some of the count outcomes will exhibit excess zeros (e.g. hospitalizations). If the counts exhibit excess zeros, we will use zero-inflated (ZI) versions of the proposed model (zero inflated Poisson and zero-inflated negative binomial [NB]) to account for the excess zeros with random effects to account for clustering by site.[55] Typically, Poisson regression is used to model count data where observations are assumed to be independent and the number of cases has variance equal to the mean for each level of the covariates. However, in practice, either the independence or equal mean and variance assumption is often violated, which can lead to over-dispersion (when the variance is greater than the conditional mean). Thus, we consider a NB model that handles the problem of over-dispersion and that does not assume an equal mean and variance assumption. In certain cases, over-dispersion may not be sufficiently modeled via the extra parameter in NB. In this case we will consider including random effects into the NB model. Zero inflated models such as ZINB can be used for modeling the excess zeros. The ZINB model is a mixture of NB model for the count part and a logit model for the excess zeros. The parameters in the ZINB model have conditional or latent class interpretations, which correspond to a susceptible subpopulation at risk for the condition (in our case ED visits/hospitalizations) with counts generated from a NB distribution and a non-susceptible subpopulation that provides the extra or excess zeros. Thus, the ZINB model parameters are not well suited for quantifying the effect of an explanatory variable in the overall mixture population. We will use a marginalized ZINB model to estimate the population mean count directly, allowing straightforward inference for overall covariate effects.[56] We will use AIC and BIC, which deal with the trade-off between the goodness of fit and complexity of the models, to choose the best fitting model among the different models; further assessment of the goodness of fit for the final model is made via the Pearson goodness of fit statistic. A model with a smaller value of AIC, BIC, and a Pearson statistic close to one is considered a better fit of the data. We will use SAS 9.4, housed within the VINCI environment, to manage the data and fit all the models.

For the cost analysis, we will also utilize multivariable modelling and propensity score

calibration (PSC).[57] We will assess the effect of the intervention on different sources of cost which include inpatient, outpatient and pharmacy in addition to the total aggregated cost. The cost models will be estimated using log-normal or gamma models (special cases of GLMM) to examine the association of the intervention with cost, adjusting for the aforementioned patient sociodemographics, donor information and transplant characteristics. Cost will be obtained from VINCI CDW and HERC as inpatient, outpatient, pharmacy and total aggregate for two years prior to the study period and for the two years of the intervention. We will also account for non-VA costs through linkage with CMS claims data. We will estimate different models adjusting for the clinical outcomes in order to examine the robustness of the results. GLMM allows for correlation between cost categories as well as for the likely skewed distribution of cost data. The Park test will be performed to check for the appropriate distribution of the cost data and AIC and BIC statistics for goodness of fit. Since, inpatient cost could exhibit a point mass of zero, we will use marginalized two-part models that are appropriate for semi-continuous data to model the relationship between the intervention and inpatient cost.[58], [59] In general, statistical analyses will use two-sided tests with alpha set at 0.05.

For the assessment of the functionality of the dashboard and the time required to complete the intervention, there will be no comparisons or modeling within this analysis; we will utilize standard descriptive statistics for these measurements, including mean (SD), median (IQR), proportion (%) and 95% confidence interval. Variables assessed for this outcome will be captured through input into the REDCap database by intervention pharmacists during the first year of the intervention. We will compile the total number of alerts the dashboard system generates at each site and assess the proportion of these that were deemed clinical relevant and actionable by the pharmacists. We will also determine the mean/median time required to complete the intervention on a daily basis and estimate the time per 100 patient days. We will conduct these assessments concurrently on a bimonthly basis for the first year of the intervention, which will allow us to modify the dashboard system's reporting thresholds and improve functionality if deemed necessary by the investigational team. We will also assess the overall functionality of the dashboard at the end of the first year to determine composite metrics. Based on our experience with the current system, after an initial bolus effect, we expect the dashboard will produce two to three new alerts per 100 patient days with one to two of these being relevant and actionable. We will utilize 95% confidence intervals actual versus expected rates.

We will handle missing data using several techniques including multiple imputation and maximum likelihood.[60] Missing data mechanisms will be examined using both univariate and multivariate methods. We will check for missing at random (MAR) by creating a missing indicator for each missing variable and study the predictors of missingness using logistic regression. If any of the fully observed covariates or outcomes becomes significant in the missing data model then we will use methods for MAR if we do not have any reason to believe that the missing data mechanism is not at random. The proposed GLMM models, which are mixed effects models for the longitudinal data analyses, can handle data that are missing at random (MAR) and provide robust estimates. For the cross-sectional data analysis plan, we will use

multiple imputation approaches and for categorical missing data we will use latent class based multiple imputation.[57,60]

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection and Management

There will two general types of data used for this proposal, which includes operational data used for the dashboard system and research data to assess the impact of the intervention on outcomes. Operational data for the dashboard will be captured through querying the national VA CDW operational database using the FRE environment and stored in VISN 7 space already approved and allocated for this project. These data elements include diagnoses, laboratory values, medication regimens, refill histories, provider types and health care encounters (hospitalizations, ER visits), gathered and queried on a daily basis. The pharmacists at intervention sites will access their site-specific dashboard information stored on the server through an end-user permission access link that will restrict which patients are visible to ensure appropriateness of access to the correct PHI.

For the research component of the proposal, data will be captured through the research CDW and housed within the VINCI environment. We will link the VA data to the SRTR registry and CMS claims data. The CDW will provide data to assess outcomes including hospitalizations, ER visits and costs, as well as mortality. CDW data will also be used to assess interventions by querying pharmacists' progress notes. The CMS data will provide non-VA health care utilization, including hospitalizations and ER visits, as well as non-VA cost estimates. The SRTR data will provide all baseline donor, recipient and transplant characteristics as well as clinical outcomes, including acute allograft rejection, graft loss and death. We will also capture pharmacist entered data, which will be their assessments of the dashboard system. We will deploy a web-based data entry system that the intervention pharmacists will use during the first year of the intervention to assess the dashboard functionality. Queries answered by intervention pharmacists will include the number of alerts received, how many were considered clinically relevant/actionable, time to conduct the intervention and general intervention types. This data will be captured through the use of the REDCap system.

After data is cleaned and completely ready for analysis, we will remove identifiers from the final datasets. This will minimize the risk of loss of confidentiality. All data will be stored on the VINCI system and only approved study personnel will have access to this data.

10.2 Quality Assurance

10.3.1 Training

Pharmacists randomized to the intervention will participate in a two-day intensive training conference held at the coordinating site (Charleston, SC). During this training, the dashboards functionality will be reviewed, along with the standard operating procedure manual which fully guides interventions. During this training conference, the intervention pharmacists will also complete competencies, using case-based questions. Pivotal sessions that occur during this conference will include: review of dashboard specifics, running the dashboard to create alerts, assessing clinical relevance of alerts, alert categories, interventions to address alerts, clinical and research documentation, provider collaboration mechanisms, motivational interviewing training and case-review sessions. The investigational team will lead these sessions and utilize local experts to deliver the presentations and lead the case-based sessions. The full training program will be developed after sites are randomized and the final dates of the training conference are agreed upon by study sites.

10.3.2 Quality Control

During the 24-month intervention period, we will have monthly teleconferences with the intervention pharmacists at the five sites to discuss and address issues with the dashboard and intervention. As an additional safety measure and to further ensure intervention fidelity, we will have experts available to discuss patient issues with sites participating in the intervention. These will include the PI, transplant nephrology, transplant hepatology and an internist. These experts are members of the study team and have full knowledge of the study. All interventions will be documented in the medical record using an approved note template, which has already been developed and is in use by pharmacists in VISN 7 and VISN 12. All interventions will be made under the approved scope of practice for the pharmacist or will be approved by the patient's VA primary care provider or other provider as appropriate. Thus, all interventions delivered as part of this study will be within usual care standards and practices.

As another quality assurance step, the coordinating site will oversee and review study interventions through querying the REDCap database system; these will be monitored by the PI and investigational team to ensure clinical appropriateness. This is particularly the case for interventions involving changes in immunosuppression regimens. If there are concerns with specific interventions made by study site pharmacists, these will be addressed on a case-by-case basis. During the course of the study, if an intervention pharmacist has a particular issue that is time sensitive and is unsure how to address it, they will have the ability to call and/or page the PI or investigational team, which includes expertise in transplant-related care. For non-urgent issues, pharmacists can send secure emails to investigational team members or bring up the issue during conference calls. Thus, there will be ample training and resources available to all intervention site pharmacists to ensure the study is conducted in a safe clinically appropriate manner with strong fidelity.

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10.3.3 Metrics

The IOC will meet and review clinical events that are related to harmful issues, which may indicate harm, including hospitalizations, ED visits, graft loss and death. The PI and study team will also review the appropriateness of study interventions, which include medication changes, discontinuations and initiations. This includes immunosuppression medications.

10.3.4 Protocol Deviations

The SOP manual is provided to study site pharmacists with detailed instructions on how to deliver the interventions, including specific protocols to use once medication safety issues have been identified. These study site interventions will be monitored by the study site and PI. If any of these interventions are deemed to be inappropriate or deviations of the SOP manual and protocols, they will be further reviewed by the study site physicians and adjudicated. Following this, if the intervention is still considered as a protocol deviation, the study site pharmacist will be informed and corrective clinical action will be taken to address the deviation. This deviation will be documented. If patterns develop in which multiple protocol deviations are occurring at a particular study site, the IOC will be informed. They will review the issues and determine a corrective plan, which may include re-education and training, replacement of the study site pharmacist or discontinuation of the study at that particular site.

10.3.5 Monitoring

During the 24-month intervention period, we will have monthly teleconferences with the intervention pharmacists at the five sites to discuss and address issues with the dashboard and intervention. As an additional safety measure and to further ensure intervention fidelity, we will have experts available to discuss patient issues with sites participating in the intervention. These will include the PI, transplant nephrology, transplant hepatology and an internist. These experts are members of the study team and have full knowledge of the study. All interventions will be documented in the medical record using an approved note template, which has already been developed and is in use by pharmacists in VISN 7 and VISN 12. All interventions will be made under the approved scope of practice for the pharmacist or will be approved by the patient's VA primary care provider or other provider as appropriate. Thus, all interventions delivered as part of this study will be within usual care standards and practices.

As another quality assurance step, the coordinating site will oversee and review study interventions through querying the REDCap database system; these will be monitored by the PI and investigational team to ensure clinical appropriateness. This is particularly the case for interventions involving changes in immunosuppression regimens. If there are concerns with specific interventions made by study site pharmacists, these will be addressed on a case-by-case basis. During the course of the study, if an intervention pharmacist has a particular issue that is time sensitive and is unsure how to address it, they will have the ability to call and/or page the PI or

investigational team, which includes expertise in transplant-related care. For non-urgent issues, pharmacists can send secure emails to investigational team members or bring up the issue during conference calls. Thus, there will be ample training and resources available to all intervention site pharmacists to ensure the study is conducted in a safe clinically appropriate manner with strong fidelity.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The VA Central IRB and VA R&Ds boards will review and approve the funded protocol, ensure protection of patient privacy and safety, and monitor the study on an ongoing basis. Serious adverse events will be reported to the VA CIRB and VA R&D as they occur. Annual reports to the VA CIRB and R&D will indicate serious adverse events, new findings that may influence continuation of the study, and reports of the IOC.

11.2 Informed Consent Forms and Procedure for Obtaining Consent

Because the randomization will occur at the site level, the participants will be the pharmacists at each of the sites. Therefore, each site pharmacist, prior to randomization, will provide written informed consent (see Appendix II for informed consent document). The informed consent process of each pharmacist will occur over the phone, between the principle investigator and each pharmacist. The informed consent document will be provided to each pharmacist prior to the call, to give them ample time to read and comprehend each component of the consent. During the consent call, the PI will review the rationale of the study, the voluntary nature of the study for each site pharmacist, the expected role, activities and duration of activities for each pharmacist and that there will be no punitive actions taken should the pharmacist not wish to continue with the study. We will ensure each pharmacist of this by also having their direct supervisor sign a letter (see Appendix III) stating this explicitly. The informed consent will also state that there are no incentives or promises provided to each pharmacist by participating in the study, including, but not limited to: promotion, salary support, increase in grade or step or co-authorship on publications that arise from this research. After the informed consent document is read and reviewed by each site pharmacist, they will be given the opportunity to ask questions about the expectations of the study. Following this, each site pharmacist willing to participate in the study will electronically sign and date the form (using their PIV-enabled signature code) and email the form back to the principle investigator using the internal VA email system and encrypting the email. The PI will then also electronically sign and date the same document using their PIV-enabled signature code, finalizing the informed consent process for that participating pharmacist.

We are requesting waiver of patient informed consent. We are also requesting waiver of HIPAA authorization for all patients. Per Federal guidelines, this research meets the requirements of minimal risk and thus waiver of informed consent may be granted through regulatory oversight if this research fulfills the following four criteria:[63,64]

1) the research involves no more than minimal risk to the subjects
2) the waiver or alteration will not adversely affect the rights or welfare of the subjects
3) the research could not be practicably carried out without the waiver or alteration
4) whenever appropriate, the subjects will be provided with additional pertinent information after participation

At the control group centers, there will be no study-related contact with the patients and thus informed consent and HIPAA authorization will not occur. Within the intervention group, those patients that are not contacted by pharmacists (no medication safety issues identified by the dashboard system) also will not provide informed consent or HIPAA authorization as no study related contact will occur with these patients. For those patients that are contacted by pharmacists as a result of a dashboard alert, the care provided is usual care that should be provided to this patient population, that is prompted by the dashboard tool. The care prompted may have also been provided in the control group in the same situation. The contact will be by phone only and pharmacists are only operationalizing the dashboard as a tool to assist in their day-to-day workflow. Given these facts, it is not practical or feasible to obtain informed consent in patients. Thus, we are requesting waiver of patient informed consent. The study is minimal risk and meets these criteria.

Ethical considerations for conducting cluster randomized studies have been thoroughly discussed and vetted within the research community. Precedent is well-established that obtaining individual-level informed consent to conduct such studies is not an absolute; and, in fact, there are numerous examples within the biomedical literature of conducting such trials with a waiver of documentation of written informed consent. Based on this literature and a review of the interventions and specifics regarding site-level randomized trials, the investigative team feels strongly that this proposal meets the four aforementioned criteria, is clearly a minimal risk study and is be capable of being safely completed with a waiver of written consent. Specifically, the research does meet Federal guidelines for minimal risk, which is “research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in the aspects of their everyday life that relate to the research.” Since the intervention is being conducted at the site-level as a clinical program, it qualifies under this definition. By having strong and thorough safeguards for protection of information and oversight of clinical care, this research will not adversely affect the rights or welfare of subjects. Because the intervention is being initiated at the site-level, in a parallel arm design, it could not practically be carried out without this waiver. Finally, we have a detailed and in-depth plan for dissemination of the results and further roll out of the intervention, which will allow patients to gain information of the potential effectiveness of this intervention after the completion of the study. Thus, this proposal meets the requirements of waiver of documentation of written informed consent and there is strong precedent from other cluster randomized trials that waiver is appropriate for this type of study design.[63-66]

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: no investigational medications will be used and all changes to patients' current medication regimens will be made in accordance with VA standards of care. The pharmacists providing the intervention will be thoroughly trained on use of the dashboard and delivery of the intervention. They will be guided by the use of protocols and a detailed standard operating procedure manual. In addition, they will have access to expert level advice from the coordinating center, which includes a transplant hepatologist, transplant nephrologist, internal medicine physician and transplant clinical pharmacy specialist with over 15 years of experience caring for transplant recipients. The interventions made during this study will be documented within the medical record and will be communicated in appropriate fashion to the Veterans' other providers. The pharmacists will work closely in a collaborative manner, with the Veteran's physicians to facilitate the management of significant medication safety issues or concerns that are identified.

11.3 Participant Confidentiality

Protection of participant confidentiality is an important component of human subject's protection. We will take careful precautions to maintain confidentiality for all participants, including both the pharmacists and patients. All research data will be electronically stored on the VINCI server, included data that is manually entered into the system via REDCap. There will be no paper data collection forms and no entry of data onto portable electronic devices or local storage devices. We will minimize the collection of PHI that which is necessary to complete the study Aims. Paper documents pertaining to this study, as required by regulatory oversight, will be stored in locked file cabinets at the Charleston VAMC Research Suite (where Dr. Taber's VA office is located). When study results are published or presented, only aggregate reports of the results will be used and Veterans' identities will not be revealed. All investigators and project personnel will also complete a certified program of instruction in the protection of human subjects in research, such as the VA website tutorial, NIH website tutorial, or the University of Miami CITI course. These courses in the responsible conduct of research and the protection of human research participants will be completed on an annual basis in compliance with institutional, PHS, and NIH regulations.

11.4 Study Discontinuation

The study will be discontinued based on the recommendations of the IOC and/or the expert transplant nephrologist opinion. These decisions will be based on bi-annual reports provided by the study biostatistician that will report SAE rates compared between the intervention and usual care groups. Discontinuation will be recommended if the intervention demonstrates increased harm or potential harm to veterans at sites randomized to the intervention. This decision will be made based on clinically or statistically significant differences that are apparent in SAE rates between intervention and usual care sites. Worrisome trends will also be considered in the IOC decision.

12 ETHICAL CONSIDERATIONS

Pharmacist participants are completely voluntary for this study. Each participating pharmacist will undergo informed written consent, with the process described in detail within section 11.2. Participating pharmacists have all the same rights as usual research participants, including the right to withdraw at any time without punitive action, the right of confidentiality of information and the right to be informed of any updated information that may impact the study or their participating in the study.

Ethical considerations for conducting cluster randomized studies have been thoroughly discussed and vetted within the research community. Precedent is well-established that obtaining individual patient-level informed consent to conduct such studies is not an absolute; and, in fact, there are numerous examples within the biomedical literature of conducting such trials with a waiver of documentation of written informed consent. Based on this literature and a review of the interventions and specifics regarding site-level randomized trials, the investigative team feels strongly that this proposal meets the four aforementioned criteria, is clearly a minimal risk study and is be capable of being safely completed with a waiver of documentation of written informed consent from each patient. Specifically, the research does meet Federal guidelines for minimal risk, which is “research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in the aspects of their everyday life that relate to the research.” Since the intervention is being conducted at the site-level as a clinical program, it qualifies under this definition. By having strong and thorough safeguards for protection of information and oversight of clinical care, this research will not adversely affect the rights or welfare of subjects. Because the intervention is being initiated at the site-level, in a parallel arm design, it could not practically be carried out without waiver of documentation of written informed consent. Finally, we have a detailed and in-depth plan for dissemination of the results and further roll out of the intervention, which will allow patients to gain information of the potential effectiveness of this intervention after the completion of the study. Thus, this proposal meets the requirements of waiver of documentation of written informed consent and there is strong precedent from other cluster randomized trials that waiver is appropriate for this type of study design.[63-66]

13 COMMITTEES

There are two groups formed specifically for the conduct of this study, which include the IOC and the pharmacists within the study sites assigned to the intervention group. The IOC will consist of the PI, co-investigators, study coordinator, data manager and consultants on the proposal. The functions of the IOC will include: 1) providing scientific oversight; 2) reviewing all serious adverse 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 IOC will meet bi-annually and as necessary by telephone. The recommendations of the IOC will be reviewed, and the PI will take appropriate corrective actions as needed. As part of this oversight, we will also recruit an

independent transplant nephrologist that is not affiliated with this study to provide their expertise and review of all study activities. The intervention group clinical pharmacist group will include the five study site clinical pharmacists that were randomly 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.

14 PUBLICATION AND DISSEMINATION OF RESEARCH FINDINGS

We plan to present the findings of these research efforts at national meetings via submission of research abstracts and also plan to publish the results of this research in several manuscripts. There are six planned manuscripts, which may increase or decrease depending on study operations and findings. The six manuscripts include the following:

1. Study design, rationale, barriers, pitfalls and solutions
2. Technical dashboard development and validation
3. Methodology paper on developing and validating a transplant cohort within the VA system
4. Primary outcomes of the clinical trial – utilization across study arms
5. Secondary costs outcomes of the clinical trial, including cost-benefit analysis
6. Descriptive paper detailing the interventions made by the clinical pharmacists and impact on process measures, including medication adherence and safety events

Authorship and author order will be discussed during conference calls. Lead authors will be identified and author panels will be decided upon during these calls. There is no promise or expectation of authorship simply from participating as a site pharmacist for this study. Disputes with authorship and order will be resolved prior to the drafting of papers and will be determined through majority consensus of the panel. We plan to disseminate the results of the research to the transplant and VA communities at large. We will work with operations partners, which include those within VISN 7 and other VISNs that provide care to significant numbers of organ transplant recipients, to develop a plan to implement the monitoring dashboard across the VA system. We will also develop a technical report for dissemination to VA leadership, which will include detailed aspects of the dashboard system, along with training and educational requirements for pharmacists and other health care professionals to utilize the system to improve the monitoring and management of Veteran organ transplant recipients. We will seek to present this information at cyber seminars and regional and national meetings and conferences, both within the formal context of research conferences and informally, through administrative and operational meetings.

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16 SUPPLEMENTS/APPENDICES

I. Appendix I - Standard Operating Procedure Manual

II. Appendix II - Informed Consent document for participating pharmacists

III. Appendix III - Letter for supervisors of participating pharmacists to sign