Multi-hospital Electronic Decision Support for Drug-associated Acute Kidney Injury (MEnD-AKI)

Study Protocol

NCT 06264752

3/6/24

1 Protocol Summary

1.1 Synopsis

Title:	Multi-hospital Electronic Decision Support for Drug-associated AKI (MEND-AKI)	
Grant Number:		
Study Description:	This is a prospective, randomized, interventional controlled trial at eight hospitals within the University of Pittsburgh Medical Center (UPMC) system. Researchers will randomize 38 hospital service clusters to receive either: 1) a Cerner electronic medication record (EMR)-based AKI passive alert which is standard of care at UPMC: this alert provides decision support within the EMR for the diagnosis and basic staging of AKI but without specific recommendations for management (Usual Care Arm); or 2) protocolized stage-based intervention delivered to the physician by a pharmacist for consideration and approval. The intervention uses an optimized automated alerting system to identify patients: 1) receiving a high-risk drug or drug combination associated with D-AKI and at low-risk (Level A) for progression to either stage 2 AKI or stage 3 AKI per KDIGO criteria and 2) patients without AKI or stage 1 AKI receiving a high-risk drug or drug combination associated with D-AKI and at high risk (Level B) for progression to either stage 2 AKI or stage 3 AKI per KDIGO criteria, and patients with AKI stage 2 or stage 3 receiving a high-risk drug or drug combination associated with D-AKI or a medication that requires renal dose adjustment. This patient specific risk-profile will be coupled with recommendations for medication management and delivered to the physician by a pharmacist for consideration and approval. Additionally, we will assess cost-effectiveness and physicians' perception of the pharmacist-led service.	
Objectives*:	Primary Objective:	Our central goal is to examine the effect of a pharmacist-led intervention augmented by clinical decision support for the early management of patients at high-risk for developing drug-associated acute kidney injury (D-AKI), progression of and short-term recovery from AKI, and on various AKI-related outcomes.
	Secondary Objectives:	

<table>
<tr><td>Endpoints*:</td><td><table>
<tr><td>Primary Endpoint:</td><td>Major Adverse Kidney Events within 30 days of randomization ($MAKE_{30}$).

Major Adverse Kidney Events within 30 days ($MAKE_{30}$) will be defined as a composite of death, new kidney replacement therapy, or final serum creatinine ≥200% of reference prior to hospital discharge and before day 30. $MAKE_{30}$ will be a dichotomous outcome.</td></tr>
<tr><td>Secondary Endpoints:</td><td>1. Progression of AKI from time of Level B intervention (first machine learning alert generated) to hospital discharge
2. AKI intensity Rate
• Duration of AKI by all stages
• Duration of AKI stage 2
• Duration of AKI stage 3
3. Nephrotoxic burden</td></tr>
</table></td></tr>
<tr><td>Study Population:</td><td>Physician-subject Inclusion: All UPMC attending physicians that belong to a primary service will be eligible for participation and will be included in the study via waiver of consent unless they opt out. The unit of randomization is hospital services (clusters). We expect to randomize 38 hospital service clusters.

Patient-subject Inclusion: All patients of UPMC attending physicians who are in the randomized hospital service clusters and receive a system alert identifying their risk for AKI progression will be included in the study via waiver of consent. Patients who do not have an alert generated will be excluded.</td></tr>
<tr><td>Phase* or Stage:</td><td></td></tr>
<tr><td>Description of Sites/Facilities Enrolling Participants:</td><td>The PI will have the support of a study team, UPMC Medical and Pharmacy Leadership, the University of Pittsburgh Department of Pharmacy and Therapeutics, and the Department of Critical Care Medicine’s CRISMA Center’s Biostatistics Data Management team to assist with the submission of regulatory documents, identification of physicians, study execution, development of the D-AKI alert system, and data storage of the de-identified datasets, respectively.

The Department of Pharmacy and Therapeutics in the School of Pharmacy is committed to leadership in pharmacy education, research, and pharmacotherapy. The department's mission is to: provide quality education that promotes problem solving and life-long learning to provide optimal and progressive pharmacy patient care ensuring safe, efficacious, and cost-effective drug use; expand the scientific knowledge base through excellence in research and foster the advancement of the profession.

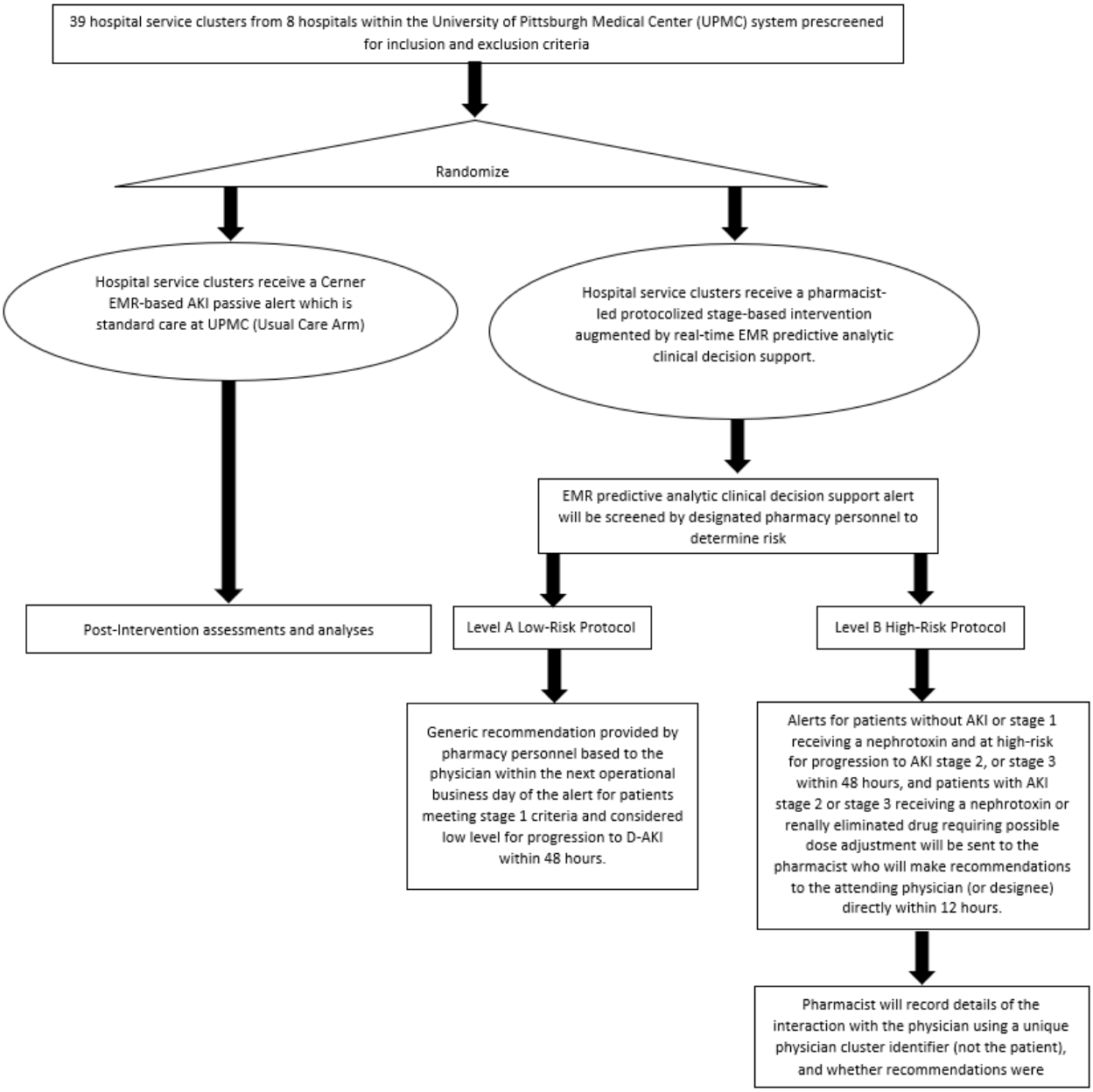
The University of Florida (UF) has very active clinical and translational research through an NIH-funded Clinical and Translational Science Institute (CTSI). The overall mission of the UF CTSI is to improve human health by accelerating the translation of scientific discoveries into practical applications and practices for the diagnosis,</td></tr>
</table>

	treatment, prevention, and cure of human diseases. It is geared to attract individual and team investigators to amplify their capabilities, and to help them more effectively and more quickly carry out their clinical and translational research. UF CTSI improvements include awarding of funding for pilot projects, changing the IRB submission process, creating new informatics resources, and introducing a common reimbursement price list for clinical research charges. The CTSI's NIH award of nearly $26 million has been matched by more than $93 million in UF commitments. The UF CTSI offers more than 40 services to UF investigators. The UF CTSI partners with other CTSAs, Florida State University, the Orlando Regional Medical Center, the North Florida/ South Georgia Veterans Health System, and the Moffitt Cancer Center.
Description of Study Intervention/ Experimental Manipulation:	The intervention will be stage-based so that stage 1 low-risk (for D-AKI) patient alerts will trigger contact with the physician within the next operational business day (Level A); and patients without AKI or stage 1 and at high-risk for AKI stage 2 or 3; stage 2; and stage 3 patient alerts will trigger direct pharmacist contact with the physician within 12 hours (Level B). A threshold of >50% will be used to differentiate between low- and high-risk for AKI progression. **Level A protocol:** the designated pharmacy personnel will screen machine learning generated CDSS alerts for redundancy and exclusion criteria using information in the EMR and clear objective criteria. The pharmacy personnel will toggle a generic recommendation based on the AKI KDIGO management guidelines to the physician within the next operational business day of receiving the alert for patients meeting stage 1 criteria and considered low level for progression to D-AKI within 48 hours. **Level B protocol:** the designated pharmacy personnel will screen machine learning generated CDSS alerts identifying patients without AKI or stage 1 receiving a nephrotoxin and at high-risk for progression to AKI stage 2, or stage 3 within 48 hours, and patients with AKI stage 2 or stage 3 receiving a nephrotoxin or renally eliminated drug requiring possible dose adjustment. Alerts for these patients will be sent to the pharmacist who will make medication management recommendations to the attending physician (or designee) within 12 hours. Recommendations may include stopping or changing a drug, changing dose or schedule, ordering laboratory tests, taking no action, or other (e.g., adding a drug, changing formulation). The pharmacy study team will only make recommendations and facilitate any actions approved/requested by the physician. Finally, the pharmacist will record details of the interaction with the physician and whether recommendations were accepted. This will be recorded using a unique physician cluster identifier (no patient identifier will be used). A Qualtrics survey will be emailed out to all UPMC physicians meeting the inclusion criteria to obtain their perception of pharmaceutical care before and after the intervention. The pre-intervention survey will be disseminated within the introductory email from the UPMC leadership. The Qualtrics link will be set-up to send reminders to the physician to complete the survey. The survey results, pre- and

	post-intervention, will be identified by a unique study identifier that cannot be linked to the responding physician.
Study Duration*:	Two years or until sample size has been reached.
Participant Duration:	Up to 24 months, as long as study is active and enrolling physicians.

1.2 Schema

Figure 1. Study Schema



1.3 Schedule of Activities

Table 1. Intervention Schedule of Activities

	Alert Received	Within 12 hours post-alert	Within next operational business day post-alert	After discussion with Physician
Level A Protocol				
Pharmacy personnel screens alert	X			
Send pre-developed recommendation to the attending physician and/or designee			X	
Level B Protocol				
Pharmacy personnel screens alert	X			
Pharmacist makes recommendations to check SCr levels		X		
Pharmacist makes recommendations to evaluate the need for additional testing		X		
Pharmacist makes recommendation about nephrotoxin management in SBAR format (change dose, check drug concentration, discontinue drug, etc.)		X		
Pharmacist makes recommendation about renally cleared medication management in SBAR format (change dose, check drug concentration, discontinue drug, etc.)		X		
Assess pharmacokinetic and pharmacodynamic drug interactions that can influence the risk of kidney injury		X		
Pharmacist provides recommendation to Physician		X		
Pharmacist modifies medication regimen based on physician approval or physician makes changes				X
Pharmacist documents intervention and acceptance of interventions				X

Table 2. Outcomes Schedule of Activities

	Pre-intervention[†]	At intervention	Post-intervention[‡]	At hospital discharge	Day 7	Day 30	Day 30 or Discharge whichever is first	Day 90	Study conclusion
Primary Outcome Evaluation									
Dialysis							X		
Death							X		
Serum Creatinine 2X reference*							X		
Secondary Outcomes Evaluation									
Progression of AKI from time of Level B intervention (first machine learning alert generated) to hospital discharge				X					
AKI intensity duration				X					
Nephrotoxic burden	X		X						
Tertiary Outcomes Evaluation									
High nephrotoxin exposure after first CDSS alert			X						
Nephrotoxic burden before and after the first Level B alert			X						
Number of inconsistently dosed renally cleared medications with UPMC approved guidelines and/or package insert		X							
Number of AKI potentiating pharmacokinetic and pharmacodynamic drug interactions		X							
Drugs that require therapeutic drug monitoring (follow UPMC protocols when available)		x							
Exploratory Outcomes Evaluation									
Physician/Pharmacist Satisfaction Survey	X								X

Cost									X
90-day mortality								X	
Progression from AKI stage at first alert of those individuals considered low-risk stage 1 (Level A)				X					
Proportion of patients with persistent AKI defined as patients with serum creatinine ≥200% of reference					X	X		X	
Change from reference serum creatinine to max peak concentration during hospital stay				X					
Length of hospital stay				X					
ICU admissions				X					
ICU-free days by day 30						X			
30-day Hospital re-admissions						X			
Hospital-free days by day 30						X			
Dialysis dependence at Day 90								X	
Alerts received in each arm									X
Pharmacist interventions (provided and completed)									X

*Reference = serum creatine value used as baseline determined based on the algorithm in Figure 2
†Pre-intervention = 12 hours before alert for nephrotoxin burden outcome and prior to start of intervention for physician survey
‡Post-intervention = 12 hours after the pharmacist has contacted the physician

2 Introduction

2.1 Study Rationale

Drug-associated acute kidney injury (D-AKI) is a major public health problem for hospitalized adults. AKI incidence has been increasing, especially in hospitalized patients and those undergoing surgery. Increased chronic and comorbid illnesses and greater use of nephrotoxic medications and imaging agents are among the most important contributing factors. Patients at high risk for AKI are repeatedly not receiving recommended diagnostic and therapeutic interventions including evaluation of potentially nephrotoxic drugs. Specifically, one-third of potential adverse drug events (ADEs) in patients with AKI are due to continuation of a contraindicated nephrotoxin. Our proposal is designed to address this

unmet need for early and appropriate management of nephrotoxins in patients at high-risk for developing D-AKI.

2.2 Background

Overall, AKI incidence in the US is estimated to be as high as 25/1000 population, greater than that of acute myocardial infarction [1]. Evidence suggests that much milder forms of AKI also are associated with increased hospital mortality risk [2-9] . While AKI affects approximately 60% of all ICU patients [10] where it is associated with mortality rates of 25-45%, it has also been shown to complicate non-ICU hospitalizations with significant worsening of short- and long-term outcomes. In one study, AKI also occurred in 11.7% of patients outside of the ICU and resulted in a 10% mortality [11]. Importantly, implementation of clinical decision support systems (CDSS) significantly improved patient outcomes. prior D-AKI is a leading cause of AKI with approximately 15-25% of AKI cases attributed to a drug[10,12,13]. The negative outcomes of D-AKI are remarkable with up to 70% of patients having residual kidney damage[14]. D-AKI can be reversible, but recovery is dependent on the duration of exposure [27]. The optimal approach is discontinuation or dose adjustment of the causative agent(s). While this may be intuitive, it can be challenging; and drug causes in early AKI stages are often missed. Remarkably, one-third of potential ADEs in patients with AKI are due to continuation of a contraindicated nephrotoxin [28].

Nephrologists are frequently not involved in the detection and initial management of patients with AKI. Equally, efforts to stem the tide of the AKI epidemic cannot rely solely on, nor require, nephrology referral for all patients because the numbers are too great. While several studies have shown that CDSS can be effective for increasing detection and reducing time to AKI detection [15-17], electronic alerts by themselves appear to have, at best, only a modest impact on clinical outcomes [11,16,18,19]. Pharmacists have successfully executed ADE prevention strategies but not in the context of previously failed AKI CDSS studies making their involvement an innovative and a key component. A pharmacy-directed intervention has already proven effective in reducing AKI in children [20]. We are proposing to deploy a predictive CDSS, and we are coupling it with a pharmacist-led, active intervention. Notably, 770,000 hospitalized patients per year are injured or die due to ADEs [21]. This stresses the need for our proposed intervention of MEnD-AKI to: 1) manage nephrotoxins early to prevent progression and possibly AKI occurrence and 2) manage renally excreted drugs to prevent subsequent ADEs.

Our study entitled “Multi-hospital Electronic Decision Support System for Drug-associated AKI” (MEnD-AKI) is an eight-hospital randomized controlled trial at the University of Pittsburgh Medical Center-UPMC to assess the effectiveness of a clinical surveillance system augmented with real-time EMR predictive analytics to support a pharmacist-led intervention to reduce the progression and complications of Drug-associated Acute Kidney Injury (D-AKI). The eight UPMC hospitals include: Altoona, Horizon, Jameson, Magee, McKeesport, Presbyterian/ Montefiore, Shadyside, and Williamsport.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The study is a protocolized stage-based intervention delivered to the physician by a pharmacist for consideration and approval vs. usual care for physicians caring for patients at risk for

developing D-AKI in the non-ICU hospital setting. The risks are expected to be minimal and include potential risk to confidentiality of physicians and patients when performing the de-identified outcome assessment, and potential for higher associated treatment and monitoring costs with the intervention. The cost of treatment will be determined based on drug acquisition, diagnosing and monitoring costs. There is the possibility of recommending a second line treatment that is less nephrotoxic than the first line treatment; however, risk vs benefit will always be assessed and the physician does not need to accept the pharmacist's recommendation. If the study pharmacist feels that the alternative dosing or drug may reduce efficacy, then this will be discussed with the physician. If there are any concerns for additional risk, the study pharmacist will recommend continued monitoring for therapeutic effect or adverse effect to the attending physician responsible for that patient's care.

2.3.2 Known Potential Benefits

Known potential benefits include:

1. By helping the physician identify a patient who is at risk for D-AKI and providing recommendations for care, the potential risk for D-AKI may be mitigated.
2. By providing predication and early management recommendations to physicians, the patients being treated may also have benefits in short- and long-term outcomes.
3. The overall costs of hospitalization could be reduced.

2.3.3 Assessment of Potential Risks and Benefits

The overall study is minimal risk. Every effort will be made to ensure that the information obtained from this study will be kept strictly confidential. UPMC and the University of Pittsburgh utilize a De-ID program that is HIPAA compliant for the de-identification of retrospective data. Despite the treatment costs potentially being higher for medications selected in the intervention group, it is believed the overall costs and monitoring will be reduced due to mitigating D-AKI events and other detrimental patient outcomes and the costs associated with these events. Additionally, the intervention detects patients at risk of D-AKI that may have not been identified and promotes the safe use of medications and prevention of patient harm. Overall, the benefits of the intervention outweigh the risks.

3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary	Major Adverse Kidney Events within 30 days of randomization ($MAKE_{30}$). **Further Detail:** Major Adverse Kidney Events within 30 days ($MAKE_{30}$) will be defined as a composite of death, new kidney	Use of $MAKE_{30}$ as an outcome in this trial is consistent with recommendations from the 2010 taskforce convened by the National Institute of Diabetes and Digestive and	Better management of nephrotoxins and reduction in nephrotoxin exposure in the intervention arm compared to the

	replacement therapy, or final serum creatinine ≥200% of reference[a] at the earliest of hospital discharge or 30 days from study enrollment, whichever occurs first. $MAKE_{30}$ will be a dichotomous outcome. Outcomes will be assessed during the index hospitalization following cluster hospital service randomization in which patients in these services will be evaluated. The components of $MAKE_{30}$ will be assessed during hospitalization until 30 days following randomization. The follow-up period will end at the earliest of death, hospital discharge or day 30, whichever occurs first. Patients who were discharged or died prior to day 30 will have a follow-up period equal to their hospital length of stay. Patients who died or were discharged after day 30 will have a follow-up period of 30 days. Patients would meet the death component of $MAKE_{30}$ if they died after hospital admission, prior to hospital discharge, and prior to day 30. Patients would meet the new kidney replacement therapy component of $MAKE_{30}$ if they presented to the hospital without end stage renal disease on chronic dialysis and then started kidney replacement therapy after hospital admission, prior to hospital discharge, and prior to day 30. Intermittent hemodialysis, continuous kidney replacement therapy, and initiation of peritoneal dialysis will all be considered new kidney replacement therapy.	Kidney Diseases to discuss trials investigating acute kidney injury [22]. For trials evaluating early interventions, the taskforce recommended a composite endpoint of death, dialysis, or a sustained loss of kidney function. One recommended option for a definition of sustained loss of kidney function was doubling of reference serum creatinine. A composite outcome is used because of the competing risks of death, new dialysis, and doubling of creatinine. Patients who die early may not progress to dialysis. Patients started on dialysis for acute kidney injury may not have persistent doubling of creatinine because of dialysis. Since publication of these taskforce recommendations, $MAKE_{30}$ defined with the same criteria as outlined in the current trial has been used as an endpoint in several clinical studies [23,24].	control arm will result in lower risk of $MAKE_{30}$. A composite outcome measure as the primary endpoint will allow for a potential increased statistical power, which in turn increases the efficiency of the trial [26]. A composite outcome bares the risk of presumed benefits for all components post-analysis, when benefits may only be relevant to one or a few of the components of the composite outcome [26].

	Patients with end stage renal disease on chronic kidney replacement therapy prior to hospitalization will be excluded in this trial. Patients would meet the persistent renal dysfunction component of $MAKE_{30}$ if they presented to the hospital without end stage renal disease on chronic dialysis and then the last serum creatinine value drawn prior to hospital discharge and before day 30 was at least twice the reference serum value. Final serum creatinine ≥200% of reference[a] will also be called persistent renal dysfunction.		
Secondary	Progression of AKI from time of Level B intervention (first machine learning alert generated) to hospital discharge **Further Detail:** Change in AKI stage at the time of the first Level B alert to hospital discharge. • We will report the % of patients who progress in stage. Progress to more severe AKI stage per the KDIGO criteria.	This will provide a measurement for comparison between kidney disease progression in the control group and the intervention group, which will provide data on whether the intervention arm experienced improved kidney outcomes over the control arm. If D-AKI and related outcomes cannot be reduced in Aim 1 then one would anticipate that severity or progression would decline.	Reduction in nephrotoxin exposure in the intervention arm compared to the control arm will result in decreased risk of new AKI and progression of AKI.
	AKI Intensity • Duration of AKI for all stages • Duration of AKI stage 2 • Duration of AKI stage 3 **Further Detail:** Duration measured as absolute number of days spent at a given AKI stage. This measure depicts a normalized duration of AKI per exposed days.	This will provide a measurement for comparison between kidney disease duration in the control group and the intervention group, which will provide data on whether the intervention arm experienced improved kidney outcomes over the control arm. If D-AKI and related outcomes cannot be	Reduction in nephrotoxin exposure in the intervention arm compared to the control arm could result in decreased nephrotoxicity and AKI severity.

	This rate measures how sustained the AKI episodes are.	reduced in Aim 1 then one would anticipate that severity or progression would decline.	
	Process outcomes **Further Detail:** **Nephrotoxic burden**- Drug.days in both study arms for those drugs considered possible/probable, probable and definitely related to AKI in <u>adult, non-ICU patients according to consensus panel</u> <u>Nephrotoxic Burden Description:</u> Global nephrotoxic exposure of patients quantified as nephrotoxic drug.days, enabling a semi-quantitative assessment of the overall nephrotoxic burden experienced by a patient, as defined a priori. With this method, each day a patient receives one nephrotoxic drug is allocated 1 point of nephrotoxic burden. Patients receiving more than one nephrotoxic drug are allocated the number of points equal to the number of nephrotoxic drugs received for that given day. For example, a patient receiving a 3-day course of acyclovir is allocated a nephrotoxic burden drug.days value of 3; a patient receiving a 3-day course of vancomycin associated with an aminoglycoside will be allocated a nephrotoxic burden drug.days value of 6. [46]	This will provide a measurement to allow analysis of effects of nephrotoxic burden on kidney outcomes for both the control group and the intervention group, which can then be compared to determine if there was improvement in process outcomes. The intervention is targeted at better nephrotoxin management so it is anticipated that burden would be improved between the pre and post assessment.	This semi-quantitative evaluation of nephrotoxic burden may overlook some differences between drugs with higher or lower kidney toxicity, but represents a pragmatic choice, easy to implement at the bedside [25].
Tertiary	**High nephrotoxin exposure** (possible/probable, probable and definite nephrotoxic medications) after the first CDSS alert (per 1000 patient days) **Further Detail:** Calculated as: number of patients with high nephrotoxic medication exposure	This will be needed to evaluate similar cases between the intervention and control group, as well as determine potential reasons for negative kidney outcomes related to nephrotoxic exposure.	Intervention will result in nephrotoxin exposure compared to control arm.

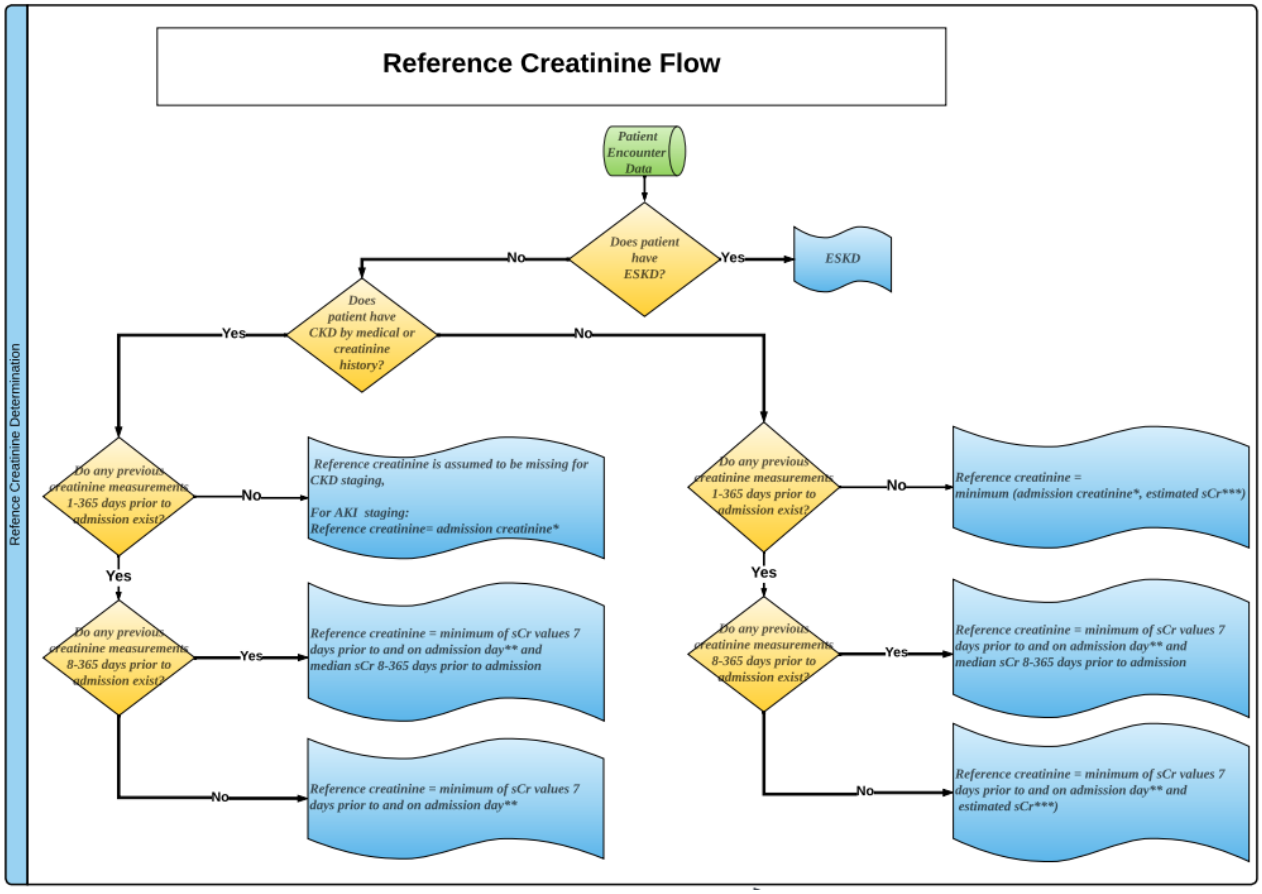
	following first CDSS alert / total number of non–critically ill patient hospital days standardized per 1000 patient-days (usual care vs intervention) Clinical meaning = This measure generates a normalized rate of high nephrotoxic medication exposure cases after risk is identified with the alert. Decreases in this measure result from decreases in high nephrotoxic medication burden in the non–critically ill population.	If the primary outcome is negative, then changing nephrotoxic burden could explain the lack of difference. Finally, this information will allow for correlation assessments between the nephrotoxic burden and $MAKE_{30}$ outcome.	
	Nephrotoxic exposure before and after the first Level B alert - number of nephrotoxins 12 hours before the intervention and then daily for each nephrotoxin rated as possible/probable (NxP rating 1.5), probable (NxP rating 2), and probable/definite (NxP rating 2.5) nephrotoxicity with routine use in adult, non-ICU patients based on clinician consensus [26].	Studies indicate a greater nephrotoxic burden result in greater nephrotoxicity.	Intervention will result in the reduction of nephrotoxin burden score compared to control arm.
	Number of inconsistently dosed renally cleared medications with UPMC approved guidelines and/or package insert. **Further Detail:** Preventable ADEs related to inconsistent dosing for a randomly selected number of patients. Preventable ADEs= a medication error resulting in harm	Studies indicate greater number of inconsistently dosed renally cleared medications result in greater nephrotoxicity.	Intervention will result in the reduction of inconsistently dosed medications compared to control arm.
	Number of AKI potentiating pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions at the time of the first Level B alert **Further Detail:** Medications administered with known PK/PD drug interactions	Increase in number of PK/PD drug interactions will result in greater D-AKI occurrence.	Intervention will result in the reduction of drug interactions compared to control arm.

	Drugs that require therapeutic drug monitoring (TDM) per UPMC protocol, (aminoglycosides, vancomycin). **Further Detail:** Number of trough/AUC concentrations considered elevated	Therapeutic drug monitoring (TDM) results in less nephrotoxicity.	Intervention will result in more therapeutic drug monitoring and lower number of patients with out-of-range drug levels in the intervention compared to control arm.
Exploratory	Physician Satisfaction/Pharmacist Satisfaction		
	Cost-effective analysis **Further Detail:** Time Pharmacist spent on making and managing intervention. Monitoring costs- therapeutic drug monitoring, additional serum creatinine monitoring Acquisition cost of drugs	We will explore whether the intervention will reduce cost associated with patient care.	This will help in determining the utility of the intervention to a hospital-system in terms of cost compared with usual care
	90-day mortality **Further Detail:** 90-day mortality (out of hospital data)	This outcome represents a different adaptation of the $MAKE_{30}$ outcome to improve our capacity to understand the impact of the proposed intervention.	This outcome will allow for longer-term data analysis and kidney outcomes than evaluating just shorter-term outcomes.
	Progression from AKI stage at first alert of those individuals considered low-risk stage 1 (Level A)	Since nephrotoxicity is reflected in the stage and severity of AKI and duration of AKI, measurement of these endpoints are critical.	Intervention is likely to reduce progression, severity and duration of AKI compared to control arm.
	Proportion of patients with serum creatinine ≥200% of reference[a] at 7 days, at 30 days and 90 days – Persistent AKI		
	Change from reference[a] to max peak creatinine during hospital stay		
	Length of hospital stay	D-AKI is associated with increased resource utilization, morbidity and mortality.	Intervention will reduce the risk and progression of D-AKI and thus result in decreased resource utilization compared to control arm.
	ICU admissions		
	ICU-free days by day 28		
	Hospital re-admissions		
	Hospital-free days by day 28		

	Dialysis dependence on Day 90	This outcome represents a different adaptation of the $MAKE_{30}$ outcome to improve our capacity to understand the impact of the proposed intervention.	This outcome will allow for longer-term data analysis and kidney outcomes than evaluating just shorter-term outcomes.
	Alerts received- Alerts received in each arm	Increase in number of alerts reflect higher likelihood of developing D-AKI.	Intervention will reduce the number of subsequent alerts in patients compared to control.
	Pharmacist intervention **Further Detail:** Pharmacist recommendation accepted. • Partial vs full acceptance • Acceptance on nephrotoxin management • Acceptance of renal dose adjustment • Acceptance of monitoring Pharmacist recommendation not accepted. • Reason for not following recommendation provided by physician	Understanding physician acceptance of the CDSS from pharmacists and physician satisfaction is critical for subsequent deployment of the intervention.	CDSS in the intervention arm will result in greater physician acceptance and physician satisfaction compared to control arm.

[a]Reference = serum creatine value used as baseline determined based on the algorithm in Figure 2.

Figure 2. Determination of Reference Creatinine Flow



This flow shows the rule for determining reference creatinine changes dynamically during the index admission. Abbreviations: ESKD, end-stage kidney disease; sCr, serum creatinine.
*Admission creatinine is the first creatinine during encounter.
** Minimum of all sCr values measured from 7 days prior to admission up to first creatinine on admission day is calculated.
***Estimated serum creatinine is calculated by back calculation from the 2021 CKD-EPI refit without race.

4 Study Design

4.1 Overall Design

This is a prospective, randomized, interventional controlled trial at eight hospitals within the University of Pittsburgh Medical Center (UPMC) system. Researchers will randomize 38 hospital service clusters to receive either: 1) a Cerner EMR-based AKI passive alert which is standard of care at UPMC: this alert provides decision support within the EMR for the diagnosis and basic staging of AKI but without specific recommendations for management (Usual Care Arm); or 2) protocolized stage-based intervention delivered to the physician by a pharmacist for consideration and approval. The intervention uses an optimized automated alerting system to identify patients: 1) receiving a high-risk drug or drug combination associated with D-AKI and at low-risk (Level A) for progression to either stage 2 AKI or stage 3 AKI per KDIGO criteria and 2) patients without AKI or stage 1 AKI receiving a high-risk drug or drug combination associated with D-AKI and at high risk (Level B) for progression to either stage 2 AKI or

stage 3 AKI per KDIGO criteria, and patients with AKI stage 2 or stage 3 receiving a high-risk drug or drug combination associated with D-AKI or a medication that requires renal dose adjustment. This patient specific risk-profile will be coupled with recommendations for medication management and delivered to the physician by a pharmacist for consideration and approval. Additionally, we will assess cost-effectiveness and physicians' perception of the pharmacist-led service.

Level A protocol: the designated pharmacy personnel will screen machine learning generated CDSS alerts for redundancy and exclusion criteria using information in the EMR and clear objective criteria. The pharmacy personnel will toggle a generic recommendation based on the AKI KDIGO management guidelines to the physician within the next operational business day of receiving the alert for patients meeting stage 1 criteria and considered low level for progression to D-AKI within 48 hours.

Level B protocol: the designated pharmacy personnel will screen machine learning generated CDSS alerts identifying patients without AKI or stage 1 receiving a nephrotoxin and at high-risk for progression to AKI stage 2, or stage 3 within 48 hours, and patients with AKI stage 2 or stage 3 receiving a nephrotoxin or renally eliminated drug requiring possible dose adjustment. Alerts for these patients will be sent to the pharmacist who will make medication management recommendations to the attending physician (or designee) within 12 hours. Recommendations may include stopping or changing a drug, changing dose or schedule, ordering laboratory tests, taking no action, or other (e.g., adding a drug, changing formulation). The pharmacy study team will only make recommendations and facilitate any actions approved/requested by the physician. Finally, the pharmacist will record details of the interaction with the physician and whether recommendations were accepted. This will be recorded using a unique physician cluster identifier (no patient identifier will be used).

During provided nephrotoxic stewardship care, if questions regarding the management of other drugs arise, study pharmacists will provide appropriate care recommendations or facilitate communication with the pharmacist affiliated with the care site.

4.2 Scientific Rationale for Study Design

A 2016 national survey of 1315 hospitals indicated that 97% have computerized order entry with clinical decision support [27]. The push for EMRs and meaningful use indicates that most institutions have technology available to implement the proposed intervention. A simpler automated alert with manual identification of at-risk patients can still be effective (automated and manual mix). Manual application of trigger tools has been applied with success; although automation does have advantages [28]. For those favoring an automated approach, our CDSS is EMR-agnostic and generates alerts directly from source data, increasing generalizability.

4.3 Justification for Intervention

Most studies assessing D-AKI focus on critically ill patients, assuming that they are at greatest risk. While it is true that patients with multiple organ failure have the highest AKI rate, lower risk categories are also affected. Low-risk patients are significantly impacted by AKI, as we have shown [29]. Furthermore, non-critically ill patients are less likely to have complex multi-etiology AKI and at the same time are less likely to be seen by pharmacists or nephrologists. Also, previous models do not emphasize drug related causes. We have already placed considerable resources to address AKI in the ICU. As an extension, our

current proposal will pair actionable alerts for non-critically ill hospitalized patients with aggressive management for D-AKI outside the ICU.

4.4 End-of-Study Definition

The end-of-study definition will be reached when adequate sample size has been achieved or after two years of the study, whichever comes first.

5 Study Population

5.1 Inclusion Criteria

UPMC attending physicians that belong to a primary service will be eligible for participation and will be automatically included in the study. The unit of randomization is physician hospital services (clusters). We expect to randomize 38 hospital service clusters.

Physician-subject Inclusion

- Physicians employed at UPMC hospital systems.
- Attending physicians of record who care for patients across multiple units.

Patient-subject Inclusion

- System alert identifying risk for AKI.
- Patient has attending physician who is participating in the randomized clusters.
- After initial patient inclusion, an individual patient will not be eligible for re-inclusion until after 90 days. Re-inclusion will only be allowed if a separate hospital admission/encounter occurs and only starting on day 91.

5.2 Exclusion Criteria

Physician-subject Exclusion

- UPMC attending physicians of record who care for ICU or ED patients.
- Hospital services excluded were transplant (heart, kidney, liver, etc.) and physician consult services (dermatology, rehabilitation, etc.).

Patient-subject Exclusion

- Patients with end stage renal disease on admission, baseline eGFR <15, comfort measures only, or died before the intervention could be delivered will be excluded.

5.3 Lifestyle Considerations

Not applicable for this study.

5.4 Screen Failures

When a system alert identifies risk for AKI for a patient of a physician-subject of this study, a screening failure might occur due to death of the patient prior to intervention, drug (nephrotoxin) discontinuation prior to intervention, and the possibility that the patient may come under the care of a different attending physician than the one that is currently being contacted for care recommendations.

5.5 Strategies for Recruitment and Retention

All UPMC attending physicians of record will receive an email summarizing the study. The study pharmacist will receive D-AKI alerts for patients of physician-subjects in hospital service clusters randomized to advanced clinical decision support. Outcomes will be measured on these patient-subjects. There is no compensation for subjects.

6 Study Intervention(s)

6.1 Study Intervention(s)

6.1.1 Study Intervention Description

This is a prospective, randomized, interventional controlled trial at eight hospitals within the University of Pittsburgh Medical Center (UPMC) system. Researchers will randomize 38 hospital service clusters to receive either: 1) a Cerner electronic medication record (EMR)-based AKI passive alert which is standard of care at UPMC: this alert provides decision support within the EMR for the diagnosis and basic staging of AKI but without specific recommendations for management (Usual Care Arm); or 2) protocolized stage-based intervention delivered to the physician by a pharmacist for consideration and approval. The intervention uses an optimized automated alerting system to identify patients: 1) receiving a high-risk drug or drug combination associated with D-AKI and at low-risk (Level A) for progression to either stage 2 AKI or stage 3 AKI per KDIGO criteria and 2) patients without AKI or stage 1 AKI receiving a high-risk drug or drug combination associated with D-AKI and at high risk (Level B) for progression to either stage 2 AKI or stage 3 AKI per KDIGO criteria, and patients with AKI stage 2 or stage 3 receiving a high-risk drug or drug combination associated with D-AKI or a medication that requires renal dose adjustment. This patient specific risk-profile will be coupled with recommendations for medication management and delivered to the physician by a pharmacist for consideration and approval. Additionally, we will assess cost-effectiveness and physicians' perception of the pharmacist-led service.

6.1.2 Administration and/or Dosing

The intervention itself is delivered to physicians but the outcomes will be measured in patients cared for by clinicians within these clusters. The decision support will be provided to the physician (or designee) on all in-patients outside the ED or ICU that he/she is caring for as the attending of record. The intervention will be stage-based so that low-risk stage 1 patient alerts will trigger contact with the physician within the next operational business day (Level A); and patients at high-risk for AKI stage 2, 3; stage 2; and stage 3 patient alerts will trigger direct pharmacist contact with the physician within 12 hours (Level B). A threshold of >50% will be used to differentiate between low- and high-risk stage 1 AKI.

Level A protocol: the designated pharmacy personnel will screen machine learning generated CDSS alerts for redundancy and exclusion criteria using information in the EMR and clear objective criteria. The pharmacy personnel will toggle a generic recommendation based on the AKI KDIGO management guidelines to the physician within the next operational business day of receiving the alert for patients meeting stage 1 criteria and considered low level for progression to D-AKI within 0-48 hours.

Level B protocol: the designated pharmacy personnel will screen machine learning generated CDSS alerts identifying patients without AKI or stage 1 receiving a nephrotoxin and at high-risk for progression to AKI stage 2, or stage 3 within 48 hours, and patients with AKI stage 2 or stage 3 receiving a nephrotoxin or renally eliminated drug requiring possible dose adjustment. Alerts for these patients will be sent to the pharmacist who will make medication management recommendations to the attending physician (or designee) within 12 hours. Recommendations may include stopping or changing a drug, changing dose or schedule, ordering laboratory tests, taking no action, or other (e.g., adding a drug, changing formulation). The pharmacy study team will only make recommendations and facilitate any actions approved/requested by the physician. Finally, the pharmacist will record details of the interaction with the physician and whether recommendations were accepted. This will be recorded using a unique physician cluster identifier (no patient identifier will be used).

Stepwise, Routine Process for Pharmacists in Managing Level B Alerts:

1. Clinical decision support alert implemented to identify patient risk (Level A or Level B)
2. Study pharmacy personnel confirms patient is eligible for intervention by utilizing the explicit criteria provided in the Case Report Form on the Web App.
3. Study pharmacist reviews patient chart to determine any intervention recommendations, such as:
    a. SCr monitoring
    b. Other laboratory monitoring
    c. Renal dose adjustment (refer to the Renally Dosed Medications table)
    d. Nephrotoxin discontinuation and alternative medication recommendation if available (utilize disease-specific guideline-based evidence for guidance)
    e. Nephrotoxicity prevention strategies (any nephrotoxin on the Nephrotoxin list that the patient is on that has toxicity prevention strategies mentioned in UpToDate or package inserts)
    f. Contrast, aminoglycosides, amphotericin B, and N-Acetylcysteine toxicity prevention and management are also mentioned in the KDIGO AKI Guidelines. Utilize all resources to provide an inclusive recommendation.
    g. Discontinuation or modification of home medications (refer to Nephrotoxin and Renally Dosed lists) Document recommendations on the Case Report Form.
4. Contact the physician and communicate recommendations using the SBAR format.
5. For physician-accepted recommendations and verbal orders, the study pharmacist will input orders into the EMR if needed within the approved policies at UPMC and within the licensure regulations for a Pennsylvania Pharmacist.
6. Document recommendation outcomes (i.e., full recommendation accepted, recommendation not accepted, etc.) on the Case Report Form.
7. Any alert interventions that require a hand-off to the next study intervention pharmacist shall be communicated securely through the designated Teams chat.
8. Any additional study communications amongst the study team will be provided in the designated Teams chat.

9. All Level B phone calls will be followed up with another phone call if the physician (or team member on the service) does not respond.
10. For any patient who was previously Level B and improves to a Level A alert at any point, the Level A protocol should be followed.

Study pharmacists will actively screen Level A and Level B alerts during normal operation hours Monday through Friday. Study pharmacists will be on-call to respond to Level B alerts over the weekends. During provided nephrotoxic stewardship care, if questions regarding the management of other drugs arise, study pharmacists will provide appropriate care recommendations or facilitate communication with the pharmacist affiliated with the care site.

6.2 Fidelity

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

For consistency, study pharmacists will receive alerts for the eight hospitals. These pharmacists will communicate with pharmacists at the eight hospitals, as appropriate. Recommendations will be documented in the web app. Study pharmacists will participate in alert development and delivery. Study pharmacists will be trained on the stepwise routine process for medication management. They will follow a checklist for Level B alerts to ensure fidelity in intervention delivery. To overcome barriers to adoption, the 5 Rights framework of CDSS [30] were applied in conceptualization and will be reconsidered throughout the development process for alerts including *right information*: evidence based medication management recommendations per guidelines and literature; *right person:* pharmacist per determination by the behavior change assessment and high risk patients; *right channels:* conferral with end-users indicate preference for both email and mobile application to deliver alerts; *right format:* determined through pilot testing prior to intervention initiation and *right point in workflow*: after preliminary assessment and the need to identify patients at risk then information should be provided as soon as available (real-time, not batched) allowing for response in the 12 hour to next operational business day window depending on level of alert. The 5 Rights are recommended by AHRQ to ensure meaningful use and successful implementation [31].

6.3 Measures to Minimize Bias: Randomization and Blinding

We are proposing an eight-hospital stratified cluster-randomized trial for the prediction of progression and early management of D-AKI. The unit of randomization is hospital service clusters of which physician groups and trainees are also included such that a given patient will be exposed to a cluster of providers all receiving either control or active intervention. We will use a commercially available pseudo-random deviate generator, (SAS Inc., Cary, NC), known to be free of serial correlations [32], to randomize hospital service clusters to the intervention in a 1:1 ratio.

6.4 Study Intervention Adherence

Study pharmacists will review alerts within the intervention group and document pharmacist actions and physician response. Adherence will be measured in two parts: 1) pharmacist adherence to the checklist of activities pre-determined in the operational manual for the intervention group and 2) physician adherence to the recommendations provided by pharmacy personnel via direct communication, not email.

6.5 Concomitant Therapy

Not applicable for this study.

6.5.1 RESCUE THERAPY

Not applicable for this study.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Generally, scenarios where discontinuation of the study intervention would be rare given the nature of the intervention and study design. However, situations in which the study intervention would not be delivered to the physician include:

- Physician leaves the UPMC health-system

7.2 Participant Discontinuation/Withdrawal from the Study

Physicians are free to withdraw (opt out of the study) at any time upon request.

7.3 Lost to Follow-Up

Physicians will be considered lost to follow-up if they leave their clinical position in the participating hospital service clusters.

8 Study Assessments and Procedures

8.1 Endpoint and Other Non-Safety Assessments

The primary study endpoint is $MAKE_{30}$. Secondary endpoints include progression of high-risk stage 1 and all-risk stage 2 AKI; AKI intensity rate based on duration (number of days) of AKI for all stages, AKI intensity rate based on duration (number of days) of AKI stage 2, and AKI intensity rate based on duration (number of days) of AKI stage 3; and overall nephrotoxic burden.

8.2 Safety Assessments

We do not anticipate any harm (or other unintended effects) to the physician study participants. The study pharmacists will be trained to deliver the interventions in adherence to and within the scope of the intervention. Intervention and control groups will differ in the presence of an advanced CDSS (intervention) versus standard Cerner AKI alert (usual care arm). Patients under the care of a hospital service assigned to the control group will receive usual care from their physician-participants without the advanced alert. There is minimal risk of confidentiality breaches for participating physicians.

8.3 Adverse Events and Serious Adverse Events

The study is a process of care intervention applying a pharmacist-led early management strategy augmented by CDSS (intervention) vs. standard Cerner AKI alert (usual care arm) for physicians of

patients in the non-ICU hospital setting at risk for developing D-AKI. The risks are expected to be minimal and include potential breach of confidentiality of physicians (and their patients) when performing the retrospective de-identified outcome assessment. Due to the nature of this study, and patient outcomes assessment being performed on retrospective collection of deidentified data, adverse events and serious adverse events are not applicable.

8.4 Unanticipated Problems

Due to the nature of this study (as per section 8.3), unanticipated problems are not applicable. However, any reports, complaints, or concerns raised by study subjects that could influence patient safety will be reported to the IRB.

9 Statistical Considerations

9.1 Statistical Hypotheses

- **Primary Efficacy Endpoint(s):** Using KDIGO criteria for staging acute kidney injury, we hypothesize that:
    - A lower proportion of patients who are cared for by providers receiving the protocolized stage-based intervention delivered by a pharmacist will experience a major adverse kidney event within 30 days of randomization ($MAKE_{30}$) compared to those cared for by providers in the Usual Care arm.
- **Secondary Efficacy Endpoint(s):**
    - A lower proportion of patients who are cared for by providers receiving the pharmacist-led intervention will progress to high-risk Stage 1 and Stage 2 acute kidney injury compared to those cared for by providers in the Usual Care arm. Moreover, a smaller number of patients, who are cared for by providers receiving the protocolized stage-based intervention delivered by a pharmacist will have a higher AKI intensity rate and nephrotoxic burden, compared to those cared for by physicians providing usual care.

9.2 Sample Size Determination

To achieve 90% power, a total of 3,000 patients are required to detect a 10% difference in $MAKE_{30}$ between the two treatment groups. This sample size estimation is based on a 3-level mixed-effects logistic regression model with level-3 randomization. In the sample size calculations, within-hospital-service and within-clinician intra-class correlations (ICCs) are assumed to be 0.02 and 0.15, respectively, and the significance level is assumed to be 0.05. The three levels include: hospital-service (level-3, the randomization level, with a total of 38 hospital-services), clinician (level-2, averaging 16 clinicians per hospital-service), and patients (level-1, averaging 4.8 patients per clinician per hospital-service).

Randomization ratio to treatment and control arms for services is 1:1, that is, half of the services within a hospital (hospital-services) will be randomized into the treatment arm and another half will be allocated to the control arm. The $MAKE_{30}$ rate is assumed to be 25% in the control arm. Under these assumptions, the study is designed to detect an effect size of 10% in $MAKE_{30}$ across the full range of scenarios described above.

9.3 Populations for Analyses

The analyses will be conducted using the intent-to-treat (ITT) principle. A secondary dose-effect analysis will be conducted based on the proportion of days a patient receives care from physicians in the intervention and control arms.

9.4 Statistical Analyses

9.4.1 General Approach

A random allocation sequence of hospital-service clusters for each hospital will be generated using a computer random number generating function based on a binomial distribution with a probability of 0.5 of receiving the intervention. If one of the intervention arms reaches 20 hospital-service clusters, the remaining hospital-services will automatically be assigned to the other arm. This block design will ensure that the resulting treatment allocation is approximately 1:1. To ensure blindness, only pseudo hospital-service numbers will be provided to the statistician for each hospital. The honest broker will keep the actual mapping (pseudo hospital-service to the actual hospital-service name). The treatment allocation will then be revealed by matching the results to the actual mapping from the honest broker. We will randomize clusters to intervention and control within strata defined by use of residents to adjust for inherent subgroup differences. The allocation sequence list will be maintained by the data management team (DMT) using a secure web-based system where assignments will be maintained and accessed by the CDSS. Pharmacists will only receive alerts from patients of physicians randomized to the intervention. Our main analysis will be intent-to-treat.

9.4.2 Analysis of the Primary Endpoint(s)

The primary hypothesis will be tested within a generalized linear mixed model (GLMM) framework. A random frailty will be added at the hospital-service cluster level and assumed to absorb extraneous sources of heterogeneity. A population-averaged estimation of the intervention effect will give the adjusted odds ratios for the main effects of the intervention. Adjusting baseline covariates include:

- Patient: age, gender, race/ethnicity, reference serum creatinine, Elixhauser Comorbidity Index or Charlson Comorbidity Index, anemia, chronic kidney disease, chronic liver disease, congestive heart failure, diabetes mellitus, hypercholesterolemia, hypertension, hypoalbuminemia, hyponatremia, malignancy, peripheral vascular disease, sepsis, surgery, trauma, insurance status, residence zip code
- Physician: service specialty, age, gender, years of Pennsylvania licensure
- Hospital: academic hospital, size (number of beds), location (urban vs rural)

Physicians declining pharmacist intervention and physician attrition are unavoidable. The GLMM framework can accommodate data missing at random. We plan to conduct a sensitivity analysis by imputing missing values using multiple imputations, specifically the random forest technique. While GLMM should provide consistent estimation results, using this imputation method may help to reduce bias and improve the precision of the estimation if the extent of missing data reduces the power by 10%.

9.4.3 Analysis of the Secondary Endpoint(s)

A GLMM with an appropriate error distribution and link function will be used to compare each of the secondary outcomes between the two intervention groups. If missing data are present, the main analysis will still employ the GLMM method among complete cases. A sensitivity analysis will be performed on multiple imputed datasets. Depending on the type of the outcome, we will employ either the random forest or Multiple Imputation by Chained Equations (MICE) technique for imputation. Rubin's rule will be used to combine the estimations from multiple imputed datasets.

9.4.4 Safety Analyses

Because the study is conducted at the physician level, safety evaluations will not be conducted at the patient level.

9.4.5 Baseline Descriptive Statistics

Descriptive statistics, both numerical and graphical, will be conducted on the outcome measures for all subjects and for each treatment group. Missing data, attrition, and noncompliance will also be examined for all subjects and by each group.

9.4.6 Planned Interim Analyses

No interim analyses are planned as we do not plan to stop the trial early. The final analyses will be conducted after all data are cleaned and the study database is locked.

9.4.7 Sub-Group Analyses

A priori subgroup analyses will be based on the following measures assessed at baseline or earlier:

- Presence of CKD (defined by eGFR < 60)
- Clinical site (a total of 8 hospitals)
- History of diabetes
- Age ≥ 65 years
- History of congestive heart failure
- ICU hospitalization (vs non-ICU)
- Sepsis during hospitalization
- Charlson comorbidity index
    - Based on the CCI score, the severity of comorbidity will be categorized into three grades: mild, with CCI scores of 1-2; moderate, with CCI scores of 3-4; and severe, with CCI scores ≥5.
- AKI stage
- History of AKI within 1 year
- Prior hospitalization within 1 year
- Social determinants of health measures

All other subgroup analyses will be considered exploratory regardless of the result.

In a GLMM model, we will incorporate the interaction between the aforementioned variable and the intervention variable to examine the effect for each subgroup. If the interaction effect is statistically significant, we will conclude that there exists a disparity in effects across levels of subgroups, defined by the corresponding variable. If the effect is not statistically significant, we will evaluate its effect size to ascertain whether the lack of significance is due to insufficient power.

9.4.8 Tabulation of Individual Participant Data

Individual participant data will not be presented.

9.4.9 Exploratory Analyses

We will conduct ancillary analyses to estimate the effect of the intervention using an alternative method which incorporates inverse probability weights into the complier-average causal effect model to address the issues of attrition and non-compliance simultaneously.

10 Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

Waivers for HIPAA authorization and informed consent have been approved by the IRB. There are no circumstances where consent will be obtained from medical patients. Consent will be implied by physicians who choose to participate voluntarily in this study.

10.1.1.2 Consent Procedures and Documentation

Physician subjects and patients under their care will be enrolled under a complete waiver of consent.

10.1.2 Study Discontinuation and Closure

There are no circumstances in which the study will be terminated or suspended early.

10.1.3 Confidentiality and Privacy

Confidentiality of patients' records will be carefully protected. The clinicians involved have usual clinical access to protected health information (PHI). All data will be secured by password-only access for the purpose of confidentiality. Patient identification will be maintained in a secure manner and will only be maintained during the interventional trial phase of the project. All retrospectively collected data will be de-identified by a certified honest broker for final analyses. The Data Manager at the CRISMA Center will act as the certified honest broker, working under a signed confidentiality agreement (UPMC/IRB Honest Broker Approval Number: HB097). The statistical analysis team will not have linkages to patient identifiers (only the certified honest broker would have such access).

Analysis of patient outcomes and costs will be performed on deidentified data and will be obtained from the EMR retrospectively in quarterly data pulls. Linkage of data to national databases (USRDS and Social Security Death Master File) will be done by an honest broker.

All data material will be maintained in locked cabinets in locked storage rooms within the department. At least two copies of all electronic data will be maintained. Access to this data is protected on several levels. First, offices are locked and secured. Second, access to computerized data are prevented by using multiple level password protection.

10.1.4 Future Use of Data

We do not currently have a data sharing plan for sharing with future investigators. If we decide to share data in the future with investigators conducting similar research both inside and outside of the University of Pittsburgh, we will contact the Office of Research before sharing de-identified research data/materials to determine whether an agreement needs to be executed. We maintain the potential for sharing the final dataset with de-identified federal repositories.

10.1.5 Key Roles and Study Governance

Principal Investigator
Sandra Kane-Gill, PharmD, MSc, FCCM, FCCP
University of Pittsburgh School of Pharmacy Pharmacy and Therapeutics
6462 Salk Hall 3501Terrace Street Pittsburgh, PA 15261
kane-gill@pitt.edu

10.1.6 Safety Oversight

Because this study is randomized at the physician level and their patients are subject to their participation in either the usual care arm (comprised of a Cerner EMR-based AKI passive alert which is standard care at UPMC) or the intervention arm (comprised of a protocolized stage-based intervention delivered to the physician by a study pharmacist using an optimized automated alerting system coupled with recommendations for patients to reduce the progression and complications of D-AKI) this is a minimal risk study. Of note, physicians are receiving recommendations and it is up to them to accept or decline.

10.1.7 Clinical Monitoring

Due to the nature of this study, clinical monitoring will not occur.

10.1.8 Quality Assurance and Quality Control

We will perform internal quality management of study conduct, data collection, documentation, and completion quarterly to ensure the study population is appropriate and study outcomes of interest are available. 5% of the study pharmacist recommendation data will be audited at 2 months, 6 months, 12

months, 18 months to ensure it is accurate and complete, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s) and with applicable regulatory requirement(s). In cases where the audit identifies discrepancies/issues, a focused education and training plan will be developed for the study pharmacist(s) and use of the readily available standardized resources will be reinforced.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

A Data and Safety Monitoring plan will be implemented by the Principal Investigator to ensure the confidentiality of the research data is being maintained during this study. Weekly or biweekly team meetings will occur to monitor the progress of the research study and to ensure the privacy and confidentiality of all study data. During the study, an established dedicated telephone number and email address will be used so that attending physicians whose clinical services are randomized to the intervention can communicate concerns regarding any aspect of the study. The voicemails and emails sent by the attending physicians will be reviewed as part of the team meetings. The following areas will be the focus of these meetings:

1) Assessment of data quality and collection

2) Identification of any concerns or issues

3) Ensure the validity and integrity of the data and whether changes to the protocol should occur as the project progresses

4) Study compliance and training

5) Ensuring confidentiality of the physician subjects in the study

10.1.9.2 Study Records Retention

Physician-subjects' patient identification will be maintained in a secure manner and will only be maintained during the interventional trial phase of the project. All data will be deidentified by an honest broker for study analysis. The honest broker will maintain a linkage file and will destroy identifiers at the earliest opportunity consistent with the conduct of research. All study documentation, whether electronic or hardcopy, will be retained for no less than seven years as per university policy.

10.1.10 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Operating Procedures (MOP) requirements. The noncompliance may be either on the part of the investigator or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Otherwise, protocol deviations/violations that occur but do not affect participant safety will be submitted with the routine safety reports as noted. Protocol deviations will be sent to the reviewing IRB per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 Publication and Data Sharing Policy

Sharing of Identifiable personal health information (PHI) will be limited to only those pharmacy clinicians who require it to complete the research and will not be reused or disclosed to any other person or entity, except as required by law, or for authorized oversight of the research project. Our institution does not permit the sharing of raw data. The results of the study will be shared with the public in the form of meeting, formal presentations, and publications.

10.1.12 Conflict of Interest Policy

The study is funded by a PHS Agency. None of the investigators identified the following as a conflict of interest:

A. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $5,000 but not $10,000?

B. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $10,000?

C. Receive remuneration (during the past or next twelve months) from a nonpublic traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $5,000 but not $10,000.

D. Receive remuneration (during the past or next twelve months) from a nonpublic traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $10,000?

E. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?

F. Receive reimbursement or sponsorship of travel expenses (for one trip or a series of trips during the past or next twelve months) by an outside entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $5,000?

G. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research and for which you are receiving royalties, milestone fees, or other proceeds that have or will exceed $5,000 but not $10,000 in any 12-month period (include payments through the University of Pittsburgh, the Veterans Administration Pittsburgh Healthcare System, UPMC, and University of Pittsburgh Physicians)?

H. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research and for which you are receiving royalties, milestone fees, or other proceeds that have or

will exceed $10,000 in any 12-month period (include payments through the University of Pittsburgh, the Veterans Administration Pittsburgh Healthcare System, UPMC, and University of Pittsburgh Physicians)?

I. Have an officer or management position with a company that either sponsors this research or owns the technology being evaluated or developed?

J. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?

10.2 Additional Considerations

Not applicable for this study.

10.3 Abbreviations and Special Terms

ADE	Adverse Drug Event
AHRQ	Agency for Healthcare Research and Quality
AKI	Acute Kidney Injury
AUC	Area Under the Curve
CCI	Charlson Comorbidity Index
CDSS	Clinical Decision Support System
CKD	Chronic Kidney Disease
CTSA	Clinical and Translational Science Awards
CTSI	Clinical and Translational Science Institute
D-AKI	Drug-Associated Acute Kidney Injury
DMT	Data Management Team
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medication Record
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonization
ICU	Intensive Care Unit
IRB	Institutional Review Board
ITT	Intention-To-Treat
KDIGO	Kidney Disease Improving Global Outcomes
MAKE	Major Adverse Kidney Event
MICE	Multiple Imputation by Chained Equations
MOP	Manual of Procedures
NC	North Carolina
NIH	National Institutes of Health
NxP	Nephrotoxicity Potential
OHRP	Office for Human Research Protections

PD	Pharmacodynamic
PHI	Personal Health Information
PHS	Public Health Service
PI	Principal Investigator
PK	Pharmacokinetic
QA	Quality Assurance
QC	Quality Control
SCr	Serum Creatinine
SOA	Schedule of Activities
TDM	Therapeutic Drug Monitoring
UF	University of Florida
UPMC	University of Pittsburgh Medical Center
US	United States
USRDS	United States Renal Data System

10.4 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

11 References

1. Ronco C, Bellomo R, Kellum J. Acute kidney injury. *Lancet*. 2019;394(10212):1949-1964.
2. Hoste E, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care*. 2006;10(3):R73 PMC1550961.
3. Kellum J, Sileanu F, Murugan R, et al. Classifying AKI by Urine Output versus Serum Creatinine Level. *J Am Soc Nephrol*. 2015;26(9):2231-2238 PMC4552117.
4. Bihorac A, Delano M, Gabrielli A, et al. Incidence, clinical predictors and outcomes of acute kidney injury among trauma patients. *J Am Soc Nephrol*. 2006;17:208A.
5. Bihorac A, Brennan M, Ozrazgat-Baslanti T, et al. National surgical quality improvement program underestimates the risk associated with mild and moderate postoperative acute kidney injury. *Crit Care*. 2013;41(11):2570-2583 PMC3812338.
6. Bihorac A, Yavas S, Subbiah S, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg*. 2009;249(5):851-858.
7. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and Mortality Associated With Postoperative Acute Kidney Injury. *Ann Surg*. 2015;261(67):1207-1214 PMC4247993.
8. Korenkevych D, Ozrazgat-Baslanti T, Thottakkara P, et al. The Pattern of Longitudinal Change in Serum Creatinine and 90-Day Mortality After Major Surgery. *Ann Surg*. 2016;263(6):1219-1227 PMC4829495.
9. Ozrazgat-Baslanti T, Thottakkara P, Huber M, et al. Acute and Chronic Kidney Disease and Cardiovascular Mortality After Major Surgery. *Ann Surg*. 2016;264(6):987-996 PMC4936961.
10. Hoste E, Bagshaw S, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015;41(8):1411-1423.
11. Al-Jaghbeer M, Dealmeida D, Bilderback A, et al. Clinical Decision Support for In-Hospital AKI. *J Am Soc Nephrol*. 2018;29(2):654-660 PMC5791078.

12. Mehta R, Pascual M, Soroko S, et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int*. 2004;66(4):1613-1621.
13. Uchino S, Kellum J, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294(7):813-818.
14. Menon S, Kirkendall E, Nguyen H, et al. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. *J Pediatr*. 2014;165(3):522-527 e522.
15. Sawhney S, Fluck N, Marks A, et al. Acute kidney injury-how does automated detection perform? *Nephrol Dial Transplant*. 2015;30(11):1853-1861 PMC4617372.
16. Colpaert K, Hoste E, Steurbaut K, et al. Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. *Crit Care Med*. 2012;40(4):1164-1170.
17. Porter C, Juurlink I, Bisset L, et al. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. *Nephrol Dial Transplant*. 2014;29(10):1888-1893.
18. Wilson F, Shashaty M, Testani J, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. *Lancet*. 2015;385(9981):1966-1974 PMC4475457.
19. Selby N, Casula A, Lamming L, et al. An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial. *J Am Soc Nephrol*. 2019;30(3):505-515 PMC6405151.
20. Goldstein S, Dahale D, Kirkendall E, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. *Kidney Int*. 2020;97(3):580-588.
21. Classen D, Pestotnik S, Evans R, et al. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. 1997;277(4):301-306.
22. Palevsky P, Molitoris B, Okusa M, et al. esign of clinical trials in acute kidney injury: Report from an NIDDK workshop on trial methodology. *Clin J Am Soc Nephrol CJASN*. 2012;7(5):844–850. doi: 10.2215/CJN.12791211.
23. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. *N Engl J Med*. 2018;378(20):1951 doi: 10.1056/NEJMc1804294.
24. McKown AC, Wang L, Wanderer JP, et al. Predicting Major Adverse Kidney Events among Critically Adults Using the Electronic Health Record. *J Med Syst*. 2017;41(10):156 doi: 10.1007/s10916-017-0806-4.
25. Ehrmann S, Helms J, Joret A, et al. Nephrotoxic drug burden among 1001 critically ill patients: impact on acute kidney injury. *Ann Intensive Care*. 2019;9(1):106. doi: 10.1186/s13613-019-0580-1.
26. Stottlemyer B, Abebe K, Fried L, et al. Expert consensus on the nephrotoxic potential of 195 medications in the non-intensive care setting: a modified-Delphi method. *Drug Saf*. 2023:1-11.
27. Pedersen C, Scheneder P, Scheckelhoff D. ASHP national survey of pharmacy practice in hospital settings: Prescribing and transcribing-2016. *Am J Health Syst Pharm*. 2017;74(17):1336-1352.
28. Tawadrous D, Shariff S, Haynes R, et al. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. *Am J Kidney Dis*. 2011;58(6):903-914.
29. Sileanu F, Murugan R, Lucko N, et al. AKI in low-risk versus high-risk patients in intensive care. *Clin J Am Soc Nephrol*. 2015;10(2):187-196 PMC4317734.
30. Campbell R. The five "rights" of clinical decision support. *J AHIMA*. 2013;84(10):42-47; quiz 48.
31. AHRQ. Section 2 - Overview of CDS Five Rights. https://digital.ahrq.gov/ahrq-funded-projects/current-health-it-priorities/clinical-decision-support-cds/chapter-1-approaching-clinical-decision/section-2-overview-cds-five-rights. Accessed June 20, 2020.
32. Meinert C. *Clinical trials*. Oxford University Press; 1986.