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Multi-Hospital Electronic Decision Support for Drug-Associated AKI

NCT 06264752

Statistical Analysis Plan

7/14/2026

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1 MEND-AKI STATISTICAL ANALYSIS PLAN - ABBREVIATION TABLE

Abbreviation	Full Term
AKI	Acute Kidney Injury
AMCP	Academy of Managed Care Pharmacy
CDSS	Clinical Decision Support System
CKD	Chronic Kidney Disease
CMO	Comfort Measures Only
CRRT	Continuous Renal Replacement Therapy
D-AKI	Drug-Associated Acute Kidney Injury
DMT	Data Management Team
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medication Record
ESRD	End Stage Renal Disease
FIN	Financial Identification Number (Hospital Stay ID)
GLMM	Generalized Linear Mixed Model
HR	Hazard Ratio
HTA	Health Technology Assessment
ICC	Intra-Class Correlation
ICU	Intensive Care Unit
IPW	Inverse Probability Weighting
IQR	Interquartile Range
ITT	Intent-to-Treat
KDIGO	Kidney Disease: Improving Global Outcomes
MAKE30	Major Adverse Kidney Events within 30 days
MAR	Missing at Random
MEnD-AKI	Multi-Hospital Electronic Decision Support for Drug-Associated AKI
MRN	Medical Record Number (Patient ID)
NCT	National Clinical Trial
NPI	National Provider Identifier
OR	Odds Ratio

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Abbreviation	Full Term
PD	Pharmacodynamic
PK	Pharmacokinetic
PPA	Per-Protocol Analysis
RR	Rate Ratio / Risk Ratio
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SD	Standard Deviation
TDM	Therapeutic Drug Monitoring
UPMC	University of Pittsburgh Medical Center
UTI	Urinary Tract Infection
Cox-PH	Cox Proportional Hazards

2 STUDY OVERVIEW

This document is the Statistical Analysis Plan for the MEnD-AKI study. The document describes the statistical methods used to analyze the primary, secondary and safety outcomes in the study. Appendix A is a list of all variables that will be analyzed in the study along with their classification and analysis method. Appendix B is the definition of all derived and composite variables and the data imputation rules for all variables where imputation is used. Appendix C shows the shell tables.

3 TRIAL SUMMARY

The overall objective of MEnD-AKI randomized trial is to examine the efficacy of an AI-based CDSS that assists in predicting acute kidney injury. Our central hypothesis is 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.

The MEnD-AKI study is a prospective, multi-center, 2-arm, stratified cluster-randomized trial, among 3000 patients with AKI across eight hospitals located at University of Pittsburgh Medical Center (UPMC) in PA. 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

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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 (Figure 2). 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.

The primary efficacy outcome is $MAKE_{30}$, which is a composite of death, new kidney replacement therapy, or final serum creatinine ≥150% of reference prior to hospital discharge and before day 30. Secondary outcomes that will be explored are progression of AKI from time of Level B intervention (first alert generated) to hospital discharge, AKI Intensity (based on duration of AKI for all stages; duration of AKI Stage 2; duration of AKI stage 3), and Nephrotoxic burden.

We will also assess, high nephrotoxin exposure (possible/probable, probable and definite nephrotoxic medications) after the first CDSS alert (per 1000 patient days), nephrotoxic exposure before and after the first Level B alert, number of inconsistently dosed renally cleared medications with UPMC approved guidelines and/or package insert, number of AKI potentiating pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions at the time of the first Level B alert, and drugs that require therapeutic drug monitoring (TDM) per UPMC protocol, (aminoglycosides, vancomycin).

Other exploratory measures include satisfaction of physicians and pharmacists, a cost-effective analysis, 90-day mortality, progression from AKI stage at first alert of those individuals considered low-risk stage 1 (Level A), proportion of patients with serum creatinine ≥150% of reference at 7 days, at 30 days and 90 days – persistent AKI, change from reference to max peak creatinine during hospital stay, length of hospital stay, ICU admissions, ICU-free days by day 30, 30-day hospital re-admissions, hospital-free days by day 30, dialysis dependence on Day 90, alerts received in each arm, and pharmacist intervention.

Analysis of secondary, tertiary, and exploratory outcomes are intended to provide supportive and descriptive evidence and will be interpreted cautiously without formal adjustment for multiple comparisons.

3.1 PATIENT INCLUSION CRITERIA

1. System alert identifying risk of AKI
2. Patient has attending physician participating in the randomized clusters
3. 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.

3.2 PATIENT EXCLUSION CRITERIA

1. End stage renal disease on admission

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2. Baseline eGFR < 15 mL/min
3. Comfort measures only
4. Discharged before intervention
5. Death before intervention
6. Admitted to ICU before intervention
7. Other misc. exclusion criteria considered non-actionable alerts, See section 3.8.3 for per protocol analysis
    a. Level A hemodynamic drug and no nephrotoxins
    b. Level A alert with no nephrotoxin and renally dosed medications dosed appropriate
    c. Renal dose appropriate
    d. No new recommendation since las alert (7d Level A, 48h Level B)
    e. Attending on alert differs and new attending not in intervention group
    f. Alert/website failure

3.3 PHYSICIAN INCLUSION CRITERIA

1. Physician employed at UPMC 8 hospital systems covering medical and surgical services of interest
2. Attending physicians of record who care for patients across multiple units

3.4 PHYSICIAN EXCLUSION CRITERIA

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

3.5 STUDY INITIATION TIME WINDOW

All patients are automatically enrolled into the trial once an alert is triggered for a physician enrolled in the trial.

3.6 ANALYTIC COHORT CREATION

In addition to the inclusion and exclusion criteria, we will exclude from ITT to PPA certain dates for which there were holidays, pre-defined breaks in trial, or other discrepancies as "Other".

We will inner join the list of included alerts with any common table expressions that derive outcome variables.

3.7 OUTCOMES

3.7.1 PRIMARY OUTCOMES

1. Major Adverse Kidney Events within 30 days of randomization ($MAKE_{30}$)

3.7.2 SECONDARY OUTCOMES

1. Progression of AKI from time of Level B intervention (first alert generated) to hospital discharge
2. AKI Intensity: Duration of AKI for all stages; Duration of AKI Stage 2; Duration of AKI stage 3

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3. Nephrotoxic burden

3.7.3 TERTIARY OUTCOMES

1. High nephrotoxin exposure (possible/probable, probable and definite nephrotoxic medications) after the first CDSS alert (per 1000 patient days)
2. Nephrotoxic exposure before and after the first Level B alert
3. Number of inconsistently dosed renally cleared medications with UPMC approved guidelines and/or package insert
4. Number of AKI potentiating pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions at the time of the first Level B alert
5. Drugs that require therapeutic drug monitoring (TDM) per UPMC protocol, (aminoglycosides, vancomycin)

3.7.4 EXPLORATORY OUTCOMES

1. Physician Satisfaction/Pharmacist Satisfaction
2. Cost-effective analysis
3. 90-day mortality
4. Progression from AKI stage at first alert of those individuals considered low-risk stage 1 (Level A)
5. Proportion of patients with serum creatinine ≥150% of reference at 7 days, at 30 days and 90 days – Persistent AKI
6. Change from reference to max peak creatinine during hospital stay
7. Length of hospital stay
8. ICU admissions
9. ICU-free days by day 30
10. 30-day Hospital re-admissions
11. Hospital-free days by day 30
12. Dialysis dependence on Day 90
13. Alerts received- Alerts received in each arm
14. Pharmacist intervention

3.7.5 SAFETY OUTCOMES

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.

3.8 SAMPLE SIZE AND MONITORING

1. 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 (hospital-service cluster) randomization. In the sample size calculations, within-

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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).

In anticipation of considerable non-actionable alerts in the intent-to-treat (ITT) analysis, approximately 3000 patients meeting criteria for actionable alerts will be included for an impactful PPA.

2. 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.
3. The analyses will be conducted using the ITT principle. As a secondary exploratory analysis, we will conduct a PPA for which we will compare individuals who have received an actionable alert to individuals in the control arm with potentially actionable alerts. We will use IPW to account for differences in probability of alerts being actionable by patient baseline characteristics.
    - Baseline characteristics include: 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
    - Hospital: academic hospital, size (number of beds), location (urban vs rural)

We will explore dose effect by adding a covariate for count of number of actionable alerts.

4 DATA ANALYSIS PLAN

4.1 OVERALL ANALYTICAL PLAN

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

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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. We will additionally perform a descriptive analysis on the alerts that were generated.

Multiplicity and interpretation of results. The primary hypothesis test pertains to the effect of the intervention on the primary outcome MAKE30 and will be conducted at a two-sided significance level of 0.05 Secondary, tertiary, and exploratory outcomes are included to characterize additional clinical effects and potential mechanisms of action of intervention. These analyses are not powered or intended for formal confirmatory inference. Therefore, their results will be interpreted as supportive or hypothesis-generating. No formal adjustment for multiple comparisons will be applied beyond the primary outcome, and nominal p-values and confidence intervals will be reported for secondary and exploratory analyses.

4.2 APPROACHES TO MODELING

General linear mixed model (GLMM) framework: We will fit a GLMM with random intercepts at the hospital-service cluster level (the unit of randomization) and at the physician level to account for the hierarchical structure of the data. Models will adjust for prespecified baseline covariates to improve precision. The GLMM estimates cluster-specific (conditional) effects, but the primary estimand is the population-averaged (marginal) intervention effect. Therefore, marginal intervention effects will be obtained from the fitted GLMM via marginal standardization, averaging predicted outcomes over the empirical distribution of the random effects and covariates. These marginal estimates will be reported as population-averaged effect measures (e.g., risk differences, risk ratios, as appropriate).

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
- Hospital: academic hospital, size (number of beds), location (urban vs rural)

The model will include random intercepts at the hospital-service and the physician levels to account for the hierarchical structure of the data, with patients nested within physicians and physicians nested within hospital-service clusters. Randomization is conducted at the hospital-service level, stratified by hospital.

Handling non-convergence:

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If the primary GLMM fail to converge, model simplification will follow a prespecified hierarchical procedure. Specifically, covariates will be considered for removal in the following order:

1. Hospital-service level contextual covariates. Examples include hospital size, urban/rural status.
2. Physician-level covariates.
3. Patient-level covariates with low prevalence or high correlation with other covariates (e.g., covariates with near collinearity).

The intervention indicator and random intercepts corresponding to the randomization unit will be retained in all models and will not be removed under any circumstances.

Any covariates removed to achieve convergence in the primary outcome model will be documented, along with the reason for removal. For secondary and tertiary outcome models, convergence issues will be addressed independently using the same prespecified hierarchy without automatically propagating exclusions across outcomes.

Continuous outcomes: A general linear mixed model (GLMM) with a gaussian distribution and identity link will be used to analyze continuous outcomes. We will use compound symmetry/exchangeable correlation structure but attempt other structures if this fails to converge.

Binary outcomes: A GLMM with a binomial distribution and logit link will be used to analyze binary outcomes. This will yield an OR as an effect.

Rate or count outcomes: A GLMM with a negative binomial distribution and a log link function. This will yield rate ratios (RR) as an effect.

The Cox Proportional Hazard Framework:

Time to event outcomes: Time-to-event outcomes will be analyzed using Cox proportional hazards models with a shared frailty term at the hospital-service level to account for within-cluster correlation. For each outcome, the time origin (time zero), event definition, and censoring rules will be prespecified and are described below. Unless otherwise noted, individuals will be administratively censored at the end of the prespecified follow-up window. Proportional hazards assumption will be assessed using standard diagnostic methods, including log-log survival plots, Schoenfeld residual plots, etc. The models will include the same set of covariates as the GLMM analyses for consistency.

4.3 DATA RULES

4.3.1 HANDLING OF DATA INCONSISTENCIES

Unstable estimates may occur with categorical covariates with few observations. We foresee issues with Zip code. If this is the case, we will use the first 3 digits of zip-code rather than all 6.

We will ensure the Included alerts dataset has no inconsistencies for inclusion or exclusion.
Check 1: We will check for all exclusion indicators to be 0 and inclusion indicator to be 1.

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Check 2: We will check all times where any exclusion indicators are 1 and the inclusion indicator to be 0. The sum of check 1 and check 2 shall be the total length of the unfiltered dataset. A discrepancy in this will require retrospective checking of the data. This can occur before or after analysis has commenced.

4.3.2 HANDLING OF MISSING DATA

The extent and patterns of missingness will be summarized by treatment arm prior to analysis.

All primary analyses will be conducted using GLMMs, which provide valid inference under the assumption that data are missing at random (MAR), conditional on observed covariates included in the model. The primary analysis will therefore be performed using complete cases, consistent with the MAR assumption and standard likelihood-based inference in GLMMs.

To assess the robustness of results to missing data, a sensitivity analysis will be conducted using imputed datasets. Missing covariate values will be imputed using a random forest-based imputation approach implemented in the MissForest package in R, which leverages nonlinear relationships and interactions among observed variables. The primary analysis model will then be refit to each imputed dataset. Results will be compared qualitatively with the complete-case analysis to evaluate sensitivity to missing data assumptions.

If no data is missing, then the sensitivity analysis will not be completed.

4.3.3 ANALYSIS DATASETS

Included alerts: This dataset shall contain alert id, hospital stay id (FIN), patient id (MRN), reason for being excluded, inclusion indicator, Alert SCr, AKI stage, and Reference creatinine

All alerts: Join the included alerts with the analytic data file:

- Patient: alert id, hospital stay id (FIN), patient id (MRN), age, gender, race/ethnicity, reference serum creatinine, Elixhauser Comorbidity Index, 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: physician service specialty, Indicator if a physician followed up and acknowledged alert
- Hospital: Academic hospital indicator, number of hospital beds, and hospital location (urban vs rural).
- Derived variables: Dialysis indicator, no AKI progressed to AKI indicator, stage 1 progressed to greater AKI indicator, stage 2 progressed to greater AKI indicator, days since randomization to death indicator, in hospital mortality indicator, maximum SCr during stay, length of stay, length of presenting AKI stage.

First alert: Select the first observation from the Included alerts file (by FIN) and join on the alert id within the All alerts dataset. This will be used for table 1.

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Nephrotoxic Burden: This dataset will include alert id, hospital stay id (FIN), patient id (MRN), Nephrotoxic burden each day of hospital stay.

4.4 ANALYSIS METHODS FOR PRIMARY OUTCOMES

4.4.1 $MAKE_{30}$

We will use the GLMM framework defined in section 4.2 with a binomial distribution and a logit link to produce an odds ratio (OR) effect.

4.4.2 PROTOCOL 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.

Physician adherence will be evaluated by acknowledgement of a recommendation. The definition of acknowledgement is pharmacist receipt of an email or call back from a physician. We will count this on the alert level and patient level.

4.4.3 RECRUITMENT RATE

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.

4.5 ANALYSIS METHODS FOR SECONDARY AND SAFETY OUTCOMES

4.5.1 PROGRESSION OF AKI FROM TIME OF LEVEL B INTERVENTION TO HOSPITAL DISCHARGE

We will use a GLMM framework (4.2) with a binomial distribution and a log link:

- High-risk patients without AKI at the time of a first level B alert who subsequently progress to maximum AKI severity stages 1, 2, or 3 before hospital discharge or 30 days, whichever comes first.
- High-risk patients diagnosed with stage-1 AKI at the time of a level B alert who subsequently progress to maximum severity stages 2 or 3 AKI before hospital discharge or 30 days, whichever comes first.
- High-risk patients diagnosed with stage-2 AKI at the time of a level B alert who subsequently progress to maximum severity stage 3 AKI before hospital discharge or 30 days, whichever comes first.

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4.5.2 AKI INTENSITY

We will use a GLMM framework (Section 4.2) with a negative binomial distribution and log link to evaluate AKI intensity, defined as the number of inpatient days spent in AKI overall and by stage. AKI intensity is treated as a count outcome with follow-up time implicitly accounted for by inpatient days. If appropriate, an offset for total inpatient days will be included to make AKI intensity as a rate.

4.5.3 NEPHROTOXIC BURDEN RATE

We will use a GLMM framework (4.2) with a negative binomial distribution and log link to evaluate:

- Nephrotoxic burden rate (5.2.1.4)

4.6 SUBGROUP ANALYSES

Prespecified subgroup analyses will be conducted to explore potential heterogeneity of the intervention effect. Subgroup analyses will be performed by including treatment-by-subgroup interaction terms in the primary analysis model for the primary outcome (MAKE30). Subgroup effects will be evaluated based on the statistical significance and magnitude of the interaction terms rather than on within-subgroup comparisons alone.

The following prespecified subgroups will be examined:

- **Severity of disease:** defined using Charleson Comorbidity Index (≥5 severe vs. <5 non-severe).
- **Receipt of alert:** defined by whether the treating physician acknowledged an alert.
- **Sepsis status:** defined by the presence or absence of sepsis at baseline.

For each subgroup, the primary analysis model will be extended to include the corresponding interaction term between treatment assignment and subgroup indicator. Results will be reported using subgroup-specific marginal effect estimates derived from the fitted GLMM models, along with confidence intervals.

All subgroup analyses are exploratory and intended to generate hypotheses regarding effect modification. No adjustment for multiple comparisons will be applied, and results will be interpreted cautiously.

4.7 SENSITIVITY ANALYSES

Missing data: To assess robustness of the primary analysis to missing data, a sensitivity analysis will be conducted using imputed datasets under the missing at random (MAR) assumption. Missing covariate values will be imputed using a random forest-based imputation approach implemented in the MissForest package in R. The results will be compared qualitatively with the primary intention-to-treat complete-case analysis.

Time to AKI recovery: Among patients with AKI at the time of the first alert, time to AKI recovery will be defined as the time from the first qualifying alert (time zero) to resolution of AKI, defined by return to no-AKI criteria. Patients will be censored at hospital discharge, death, or 30 days, whichever occurs first. Cox proportional hazards model with a shared frailty term at the hospital-service level will be used. Data will be restricted to patients whose treating physicians adhered to the assigned intervention status.

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Time to change in Nephrotoxic burden: Among individuals with Nephrotoxin burden > 0 at the time of the first alert, time zero will be defined as the date of the first alert and the event will be a reduction in Nephrotoxic burden by at least one agent. Among individuals with Nephrotoxin burden = 0 at the time of first alert, the event will be initiation of any Nephrotoxin medication. Patient will be censored at hospital discharge, death, or 30 days, whichever occurs first. Analysis will be conducted using Cox proportional hazards frailty models.

90-day mortality: Time to death will be measured from randomization (time zero) to death from any cause. Patients alive at 90 days will be administratively censored at day 90. This analysis will be conducted using a Cox proportional hazards frailty model.

Length of hospital stay: Time to hospital discharge will be measured from randomization (time zero). Death prior to discharge will be treated as a censoring event. As a sensitivity analysis, death will be treated as a competing event. In addition, length of hospital stay will be analyzed as a count outcome using a GLMM with a log link and Poisson or negative binomial error distribution, as appropriate based on model fit.

Dose-effect analysis: To explore the relationship between intervention exposure intensity and outcomes, we completed a per-protocol analysis.

Exposure will be quantified as the proportion of inpatient days during which a patient was under the care of physicians assigned to the intervention arm, categorized into actionable or non-actionable. This analysis will be conducted under an as-treated framework, using regression models analogous to the primary analysis, with IPW weighting for baseline covariates. Because intervention exposure is post-randomization and may be influenced by patient characteristics and clinical course, results from this analysis will be interpreted as associational and hypothesis-generating, rather than causal. We will add a covariate counting the number of actionable alerts for the dose effect.

Except for the dose-effect analysis, the above-mentioned sensitivity analyses will be conducted primarily under the intention-to-treat (ITT) framework to assess robustness of the primary findings to modeling assumptions and data limitations. Additional per-protocol and as-treated analyses will be conducted as secondary sensitivity analyses to explore the effect of actual intervention exposure and adherence.

5 APPENDICES

5.1 APPENDIX A: OUTCOME VARIABLES AND ANALYSIS METHOD

Variable	Outcome Category	Scale	Analysis Method
Major Adverse Kidney Events within 30 days of randomization ($MAKE_{30}$) MAKE30 Vs No MAKE30	Primary	Binary (OR)	GLMM
Progression of AKI from time of Level B intervention (first	Secondary	Binary (OR)	GLMM

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alert generated) to hospital discharge Progression Vs. Did not progress			
AKI Intensity: Duration of AKI for all stages; Duration of AKI Stage 2; Duration of AKI stage 3 Length stage 1; Length stage 2; Length stage 3	Secondary	Count/Rate	GLMM
Nephrotoxic burden rate	Secondary	Continuous (RR)	GLMM
High nephrotoxin exposure (possible/probable, probable and definite nephrotoxic medications) after the first CDSS alert (per 1000 patient days)	Tertiary	Binary or Categorical	GLMM
Nephrotoxic exposure before and after the first Level B alert	Tertiary	Binary	GLMM
Number of inconsistently dosed renally cleared medications with UPMC approved guidelines and/or package insert	Tertiary	Continuous	Descriptive
Number of AKI potentiating pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions at the time of the first Level B alert	Tertiary	Continuous	Descriptive
Drugs that require therapeutic drug monitoring (TDM) per UPMC protocol, (aminoglycosides, vancomycin)	Tertiary	Continuous	Descriptive
Physician Satisfaction/Pharmacist Satisfaction	Exploratory	Qualitative	Qualitative
Cost-effective analysis	Exploratory	Model	Model
90-day mortality	Exploratory	Binary	GLMM
Progression from AKI stage at first alert of those individuals considered low-risk stage 1 (Level A)	Exploratory	Binary (OR)	GLMM
Proportion of patients with serum creatinine ≥150% of reference at 7 days, at 30 days and 90 days – Persistent AKI	Exploratory	Binary	GLMM

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Change from reference to max peak creatinine during hospital stay	Exploratory	Continuous	GLMM
Length of hospital stay	Exploratory	Continuous	Cox-PH
ICU admissions	Exploratory	Binary	GLMM
ICU-free days by day 30	Exploratory	Continuous	GLMM
30-day Hospital re-admissions	Exploratory	Binary	GLMM
Hospital-free days by day 30	Exploratory	Continuous	GLMM
Dialysis dependence on Day 90	Exploratory	Binary	GLMM
Alerts received- Alerts received in each arm	Exploratory	Binary	T-test
Pharmacist intervention (Positive physician acknowledgement of alerts)	Exploratory	Binary	T-test

5.2 APPENDIX B: DERIVED VARIABLES

5.2.1 OUTCOME VARIABLES

5.2.1.1 $MAKE_{30}$

The $MAKE_{30}$ variable is defined as a composite of composite of death, new kidney replacement therapy, or final serum creatinine ≥150% of reference prior to hospital discharge and before day 30. Variables necessary for calculating this include death rate, CRRT ultrafiltrate (mL/hr) with datetime, CRRT dialysis flow rate with datetime, CRRT actual patient fluid removal with datetime, reference serum creatinine from model, and serum creatinine labs with datetime (Cerner or pharmacist reported most recent lab value). The timeframe evaluated will be 30 days from study enrollment to discharge, whichever is first.

5.2.1.2 Progression of AKI from time of Level B intervention to hospital discharge

Percentage of high-risk patients without AKI at the time of a first level B alert who subsequently progress to maximum AKI severity stages 1, 2, or 3 before hospital discharge or 30 days, whichever comes first.

Percentage of high-risk patients diagnosed with stage-1 AKI at the time of a level B alert who subsequently progress to maximum severity stages 2 or 3 AKI before hospital discharge or 30 days, whichever comes first.

Percentage of high-risk patients diagnosed with stage-2 AKI at the time of a level B alert who subsequently progress to maximum severity stage 3 AKI before hospital discharge or 30 days, whichever comes first.

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This is calculated using the reference serum creatinine, initial stage, and max SCr during intervention.

5.2.1.3 AKI intensity rate

AKI intensity is operationalized as the count of inpatient days during which a patient meets AKI criteria, overall and by stage.

Variable	Definition	Encoding
AKI_ANY_DAYS	Number of days that a pt has any AKI. Days = COUNT of ADMIT_DAYS with AKI_STAGE = 1/2/3	Days
AKI_STAGE1_DAYS	Number of days that a pt has any AKI. Days = COUNT of ADMIT_DAYS with AKI_STAGE = 1	Days
AKI_STAGE2_DAYS	Number of days that a pt has any AKI. Days = COUNT of ADMIT_DAYS with AKI_STAGE = 2	Days
AKI_STAGE3_DAYS	Number of days that a pt has any AKI. Days = COUNT of ADMIT_DAYS with AKI_STAGE = 3	Days

This is divided into three categories: Duration of AKI for all stages, duration of AKI for stage 1 , duration of AKI for stage 2, and duration of AKI for stage 3.

In the subgroups, the intensity will be based on the initial stage of AKI the patient presents with during randomization. Rate calculation example: if someone presents with stage 3 on day 1 then progress to stage 1 on day 2, then has no AKI on day 5, then discharged on day 7. Duration of any AKI will be 5 days, while duration of stage 3 will be counted as 1 day. Both denominators would be 7.

Variables needed to calculate the intensity are if a patient had an AKI, possible AKI alert (Cerner passive alert), reference serum creatinine from the model, and serum creatinine labs with datetime.

5.2.1.4 Nephrotoxic burden rate

Variables needed to assess this are the nephrotoxic medications (Cerner and the Webapp) and medication administration with datetime. The numerator is the aggregate number of unique nephrotoxic drugs administered in a day counted for all days since randomization. The denominator is time the individual was in-patient (or max 30 days) during the entire trial period.

5.2.2 EXPLORATORY VARIABLES

We will use following criteria to discuss details about exploratory variables.

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5.2.2.1 Physician satisfaction/Pharmacist satisfaction

A survey will be completed by the physicians who have participated in the trial.

5.2.2.2 Cost-effective analysis

The primary plan for the cost-effective analysis is to determine whether the intervention will reduce cost associated with patient care.

5.2.2.3 Pharmacist intervention

Pharmacist intervention will be measured when a recommendation is accepted or rejected. Alerts with unsure acceptance will be excluded. The amount alerts that were positively acknowledged by the physicians will be measured if partial or complete. The types of recommendations that will be evaluated for acceptance are partial vs complete acceptance, acceptance of intervention on nephrotoxin management, acceptance of renal dose adjustment, and acceptance of monitoring. A qualitative summary of reasons for declining recommendation from a physician will occur.

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5.3 APPENDIX C: SHELL TABLES

5.3.1 TABLE 1: CHARACTERISTICS OF PATIENTS AT BASELINE

Characteristics	No. (%)	
	Control (N= XX)	CDSS intervention (N=XX)
Age, years, median (IQR)		
Female sex		
Actual body weight, Kilograms, median (IQR)		
Baseline serum creatinine, mg/dL, median (IQR)		
Reference serum creatinine, mg/dL, median (IQR)		
Estimated glomerular filtration rate, mL/min/1.73m^2 median (IQR)		
Age ≥ 65		
Pre-existing conditions		
Diabetes mellitus		
Heart failure		
Elixhauser Comorbidity index		
Charleson Comorbidity Index score		
Mild (score 1-2)		
Moderate (score 3-4)		
Severe (score ≥ 5)		
Baseline SCr used for calculating AKI		
No AKI		
Stage 1		
Stage 2		
Stage 3		
AKI stage on admission		
No AKI		
Stage 1		
Stage 2		
Stage 3		
Maximum AKI stage reached		
No AKI		
Stage 1		
Stage 2		
Stage 3		
History of AKI in past year		
Prior hospitalization in past year		
Clinical Site		
Altoona		

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Characteristics	No. (%)	
	Control (N= XX)	CDSS intervention (N=XX)
Horizon		
Jameson		
Magee		
McKeesport		
Presbyterian		
Shadyside		
Williamsport		
Clinical condition during study enrollment		
Sepsis		
AKI		
UTI		
Trauma		
Surgery within 48 hours of admission		
Insurance status		
Uninsured		
Medicaid		
Medicare		
Private payer		

5.3.2 TABLE 2: EXCLUDED PATIENTS

Characteristics	No. (%)	
	Control (N= XX)	CDSS intervention (N=XX)
Age		
Sex		
CKD		
ICU		
Clinical Site		
Altoona		
Horizon		
Jameson		
Magee		
McKeesport		
Presbyterian		
Shadyside		
Williamsport		

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5.3.3 TABLE 3: PRIMARY AND SECONDARY OUTCOMES

		Unadjusted Analysis			Adjusted Analysis			
	Outcomes	**Control (N= XX)**	**CDSS intervention (N=XX)**	**P value**	**OR / RR / Beta**	**LL of 95% CI**	**UL of 95% CI**	**P value**
Primary								
	$MAKE_{30}$, mean (SD)	X/XX (X.X%)	X/XX (X.X%)	Chi-sq / Mann Whitney / T test				
Secondary and Tertiary outcomes								
	Progression of AKI from time of Level B intervention (first alert generated to hospital discharge)							
	AKI Intensity: Duration of AKI for all stages; Duration of AKI Stage 2; Duration of AKI stage 3							
	Nephrotoxic burden[#]							
	High nephrotxin exposure (possible/probable, probable and definite nephrotoxic medications) after the first CDSS alert (per 1000 patient days)							
	Difference in Nephrotoxic burden before and 72 hours after the first Level B alert[#*]							
	No AKI							
	Stage 1							
	Stage 2							
	Stage 3							

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Outcomes	Unadjusted Analysis			Adjusted Analysis			
	Control (N= XX)	CDSS intervention (N=XX)	P value	OR / RR / Beta	LL of 95% CI	UL of 95% CI	P value
Number of inconsistently dosed renally cleared medications with UPMC approved guidelines and/or package insert							
Antimicrobial UPMC renally adjusted medications							
Non-antimicrobial UPMC renally adjusted medications							
Anticoagulants							
Other							
Exploratory outcomes							
90-day mortality							
Progression from AKI stage at first alert of those individuals considered low-risk stage 1 (Level A)							
Proportion of patients with serum creatinine ≥150% of reference at 7 days, at 30 days and 90 days – Persistent AKI							
Change from reference to max peak creatinine during hospital stay							
Length of hospital stay							
ICU admissions							
ICU-free days by day 30							
Dialysis dependence on Day 90							
Alerts received- Alerts received in each arm			[redacted]				
Level A							

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Outcomes	Unadjusted Analysis			Adjusted Analysis			
	Control (N= XX)	CDSS intervention (N=XX)	P value	OR / RR / Beta	LL of 95% CI	UL of 95% CI	P value
No AKI							
Stage 1							
Level B							
No AKI							
Stage 1							
Stage 2							
Stage 3							
Acceptance of intervention							
Complete							
Partial							
Acceptance of intervention on nephrotoxin management							
Complete							
Partial							
Acceptance of intervention on renal dose adjustment							
Complete							
Partial							
Physician positively acknowledged alerts							
Level A							
No AKI							
Stage 1							
Level B							
No AKI							
Stage 1							
Stage 2							

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		Unadjusted Analysis			Adjusted Analysis			
	Outcomes	**Control (N= XX)**	**CDSS intervention (N=XX)**	**P value**	**OR / RR / Beta**	**LL of 95% CI**	**UL of 95% CI**	**P value**
	Stage 3							

$ Adjusted for differences in 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. Also adjusted for physician service specialty, age, gender, years of Pennsylvania licensure. Also adjusted for hospital-- academic hospital, size (number of beds), location (urban vs rural)

Burden = Calculated by count unique nephrotoxic medications per day

*Those who move from non-ICU to ICU are excluded from this calculation

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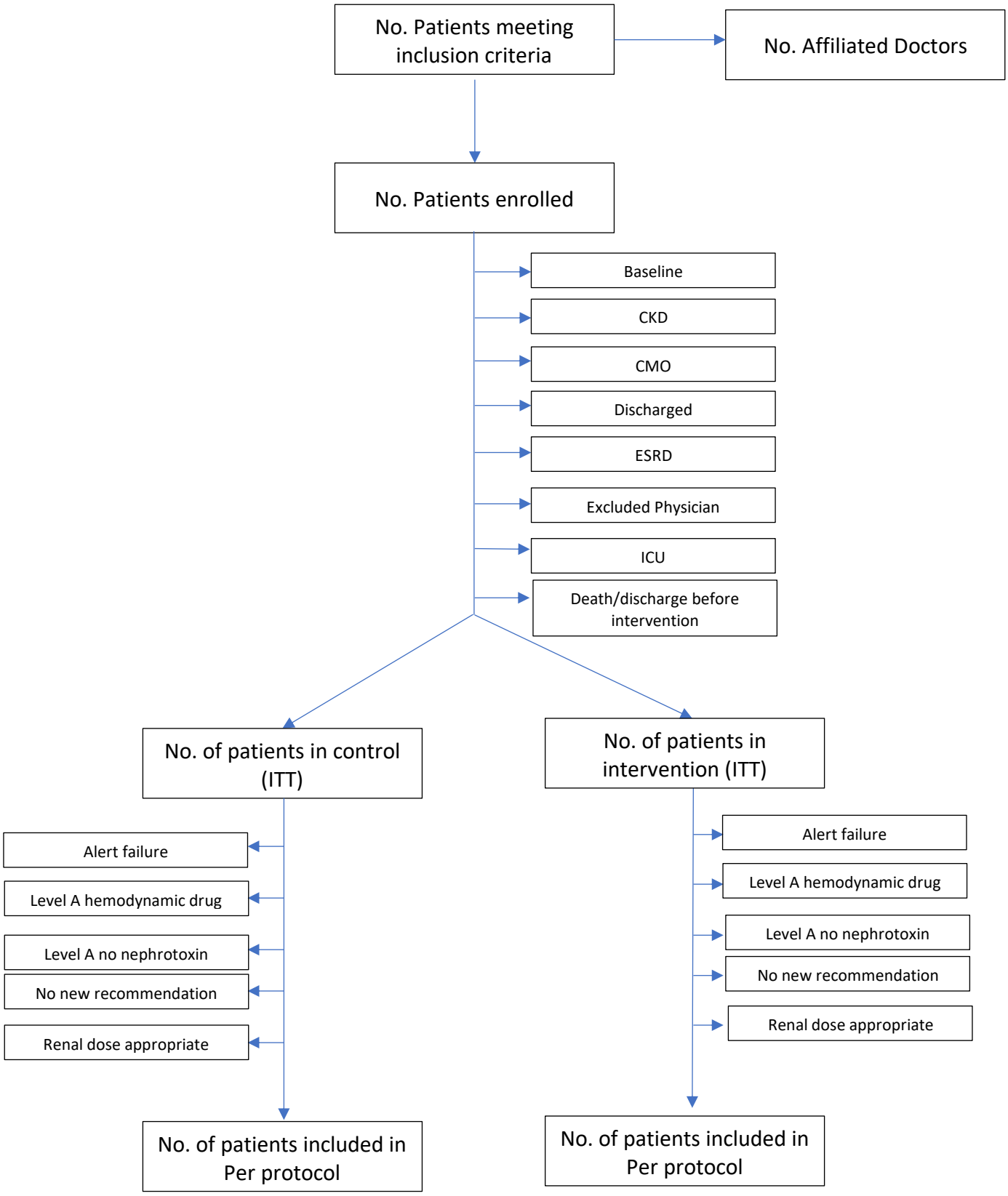
5.3.4 TABLE 4: PHYSICIAN DEMOGRAPHICS

Characteristics	No. (%)		Unadjusted P value
	Control (N= XX)	CDSS intervention (N=XX)	
Age			
Physician Type			
Family Medicine			
General Medicine			
General Surgery			
Hospitalist			
Obstetrics Gynecology			
Psychiatry			
Orthopedic Surgery			
Cardiology			
Neurology			
Neurosurgery			
Pulmonary Medicine			
Cardiac Surgery			
Hematology/Oncology			
Surgical Oncology			
Hospital			
Altoona			
Horizon			
Jameson			
Magee			
McKeesport			
Presbyterian			
Shadyside			
Williamsport			

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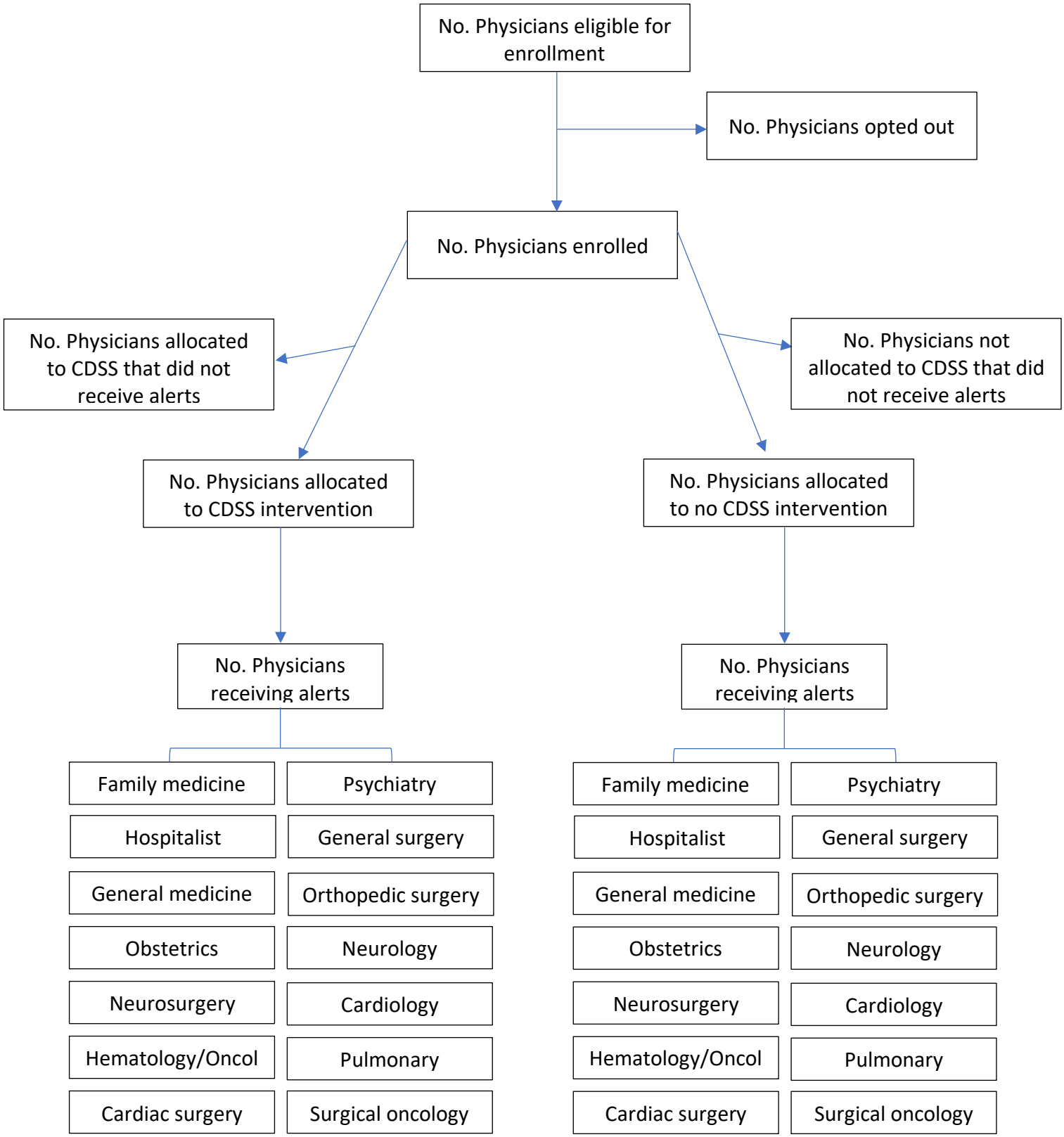
5.4 APPENDIX D

5.4.1 FIGURE 1: PATIENT FLOW THROUGH THE TRIAL



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5.4.2 FIGURE 2: PHYSICIAN ENROLLMENT FLOWCHART



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5.4.3 FIGURE 3: ALERT DESCRIPTIONS THROUGH TRIAL

