# Personalized Recommendations for Acute Kidney Injury (AKI) Care Using a Kidney Action Team: A Randomized Trial

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**CLINICAL STUDY PROTOCOL**

# Protocol Title: Personalized Recommendations for Acute Kidney Injury (AKI) Care Using a Kidney Action Team: A Randomized Trial

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# Synopsis

**Primary Objective**

This is a clinical trial designed to determine whether personalized recommendations for the workup and treatment of patients with Acute Kidney Injury (AKI) will improve the rates of AKI best practices and reduce the rates of inpatient dialysis, inpatient mortality and AKI progression in a hospitalized population.

**Study Duration**

We anticipate approximately 36 months in which patients are randomized and data is collected, followed by 6 months of data analysis activities and publication.

**Study Design**

This is a randomized, controlled, single-blind, multicenter clinical trial.

**Study Population**

Adult inpatients within the Yale New Haven Health System who meet the following criteria:

*Inclusion Criteria:*

1. Adults ≥ 18 years admitted to a participating hospital
2. Stage 1 Acute Kidney Injury as defined by KDIGO creatinine criteria:
    a. 0.3 mg/dl increase in inpatient serum creatinine over 48 hours OR
    b. 50% relative increase in inpatient serum creatinine over 168 hours

*Exclusion Criteria:*

1. Admission to hospice service or comfort measures only order
2. Recipient of a solid organ transplant
3. Immediate dialytic indication determined by the following:
    a. K ≥7 meq/L
    b. Acute ingestion of dialyzable toxin
    c. Refractory volume overload
    d. BUN > 150 mg/dL
    e. pH < 7.15 despite ventilatory support
4. Pre-existing CKD stage 5 or ESKD
5. Initial hospital creatinine > 4.0 mg/dl
6. Nephrology already consulted
7. Status post nephrectomy (partial or radical) during index admission

**Number of Participants**

The study will enroll 4,000 individuals.

**Number of Study Sites**

The study will occur across two health systems and 7 study sites.

1) The Yale New Haven Health System, comprising five hospitals in Connecticut and Rhode Island: Yale New Haven Hospital, Bridgeport Hospital, Greenwich Hospital, Lawrence and Memorial Hospital, and Westerly Hospital.

2) Two hospitals in the Johns Hopkins Hospital System: Johns Hopkins Medical Center and Johns Hopkins Bayview

**Primary Outcome Variables**

The primary outcome will be a composite of progression of AKI, Dialysis, and death at 14 days post randomization or at hospital discharge, whichever comes first. Progression of AKI is defined as a higher KDIGO-creatinine stage than that present at the time of randomization. Dialysis is defined by the receipt of hemodialysis, continuous renal replacement therapy, or peritoneal dialysis. Isolated ultrafiltration treatments for the purpose of volume removal will not be included.

**Secondary and Exploratory Outcome Variables (if applicable)**

Several secondary outcomes will be assessed as follows:

-Inpatient mortality rate within 14 days

-Inpatient dialysis rate within 14 days

-Inpatient progression of AKI within 14 days

-The percent of discrete recommendations followed within 24 hours of randomization

-The rate of kidney consult within 14 days

-Rates of discharge to hospice care

We will also perform an assessment of heterogeneity of treatment effect across the study sites, as it is possible that the benefit of the KAT depends not only on patient characteristics, but upon local resources and practices.

# 1 - Introduction

### 1.1 Introductory Statement

This is a clinical trial designed to determine whether personalized recommendations for the workup and treatment of patients with Acute Kidney Injury (AKI) will improve the rates of AKI best practices and reduce the rates of inpatient dialysis, inpatient mortality and AKI progression in a hospitalized population.

# 2 - Background

### 2.1 Clinical Experience

Acute Kidney Injury (AKI), defined as an abrupt loss in kidney function, is common, occurring in 5-20% of hospitalized patients, and carries a significant and independent risk of inpatient mortality of up to 20% in some studies, even with small increases in serum creatinine concentration.[1-6] If left untreated, AKI may significantly increase the risk of chronic kidney disease, the need for dialysis, and long-term mortality.[7-9]

Despite such effects on morbidity and mortality, the incidence of AKI is increasing and clinical trials have yet to find an intervention that can be broadly implemented as an AKI treatment.[10-11] Thus, international guidelines for the treatment of AKI focus on "best practices" that include appropriate management of drug dosing, the avoidance of kidney-toxic exposures, and careful assessment of fluid and electrolyte balance.[2] Management relies on three pillars of care: recognition, diagnostic workup, and a patient-specific treatment plan. Early recognition of AKI and early nephrologist involvement may improve clinical outcomes.[3] However, AKI, which is often asymptomatic, is frequently overlooked in a variety of hospital settings.[1,12-13] In a previous study, we showed that only 43% of patients at a tertiary care academic hospital had documentation of their AKI in the medical record, and that missed documentation was associated with increased mortality after adjusting for admission type and severity.[14] Perhaps more concerning, our group and others have shown that patients often continue to be exposed to kidney-toxic medication after AKI onset.[15-16] Other AKI "best practices", such as urinalysis and further laboratory work-up, occur inconsistently and in a small minority of patients with AKI.[17-19]

Previous studies by our group have focused extensively on increasing provider awareness and recognition of AKI. Our group conducted a randomized clinical trial testing the efficacy of electronic alerts for AKI.[20-21] This trial randomized 2,373 patients with AKI to usual care, or to an alert group in which a single alert was sent to the patient's primary provider. This alert was to make providers aware of the presence of AKI, however, it did not describe or offer specific actions a provider could take in response to the alert. We demonstrated clinical equipoise regarding the effectiveness of such alerting, as there was no improvement in the rates of AKI progression, dialysis or mortality among those in the alert group.

Rather than simply making providers aware of AKI, it may be beneficial to provide them with actionable items to aid in the care of their patients. Because of the heterogeneity of both the AKI patient population and AKI etiology, diagnostic and treatment plans must be highly individualized. Such plans must consider many facets of care, including changes to and careful monitoring of prescribed medications, optimization of hemodynamics, and management of complications. Despite the apparent complexity, we believe that individualized plans are amenable to highly protocolized interventions that can be delivered in a timely manner. Our aim in this study is to determine, through a randomized multicenter clinical trial, if personalized recommendations for the work-up and treatment of AKI will improve patient outcomes. Patients with AKI will be identified in real-time, upon which a "Kidney Action Team" will be alerted. The Kidney Action Team will be composed of an

advanced practitioner and a pharmacist, and overseen by a nephrologist, and trained to provide real-time recommendations for AKI work-up and management within one hour of AKI onset. Patients will be randomized to either receive usual care, or to an active intervention group in which the recommendations of the Kidney Action Team are delivered to the patient's primary care team. Our primary outcome will be a composite of AKI progression, dialysis and death at 14 days post-randomization, while process outcomes will focus on the amount of recommendations implemented within 24 hours of delivery. The highly protocolized and objective nature of AKI recommendations will allow for multiple independent Kidney Action Teams across multiple study sites, and, should this intervention prove successful, will provide a highly generalizable model for easy integration into other health systems. Further, because of their highly algorithmic nature, the recommendations are amenable to automation, and our results may warrant future research to create and validate an automated clinical decision support system that will efficiently identify AKI patients and provide highly individualized and timely treatment plans without the need for a Kidney Action Team.

### 2.2 Background/prevalence of research topic

Rapid response teams have proliferated, but no rapid response team for AKI has been evaluated. In 2008, the Joint Commission National Safety Goal required hospitals to implement systems to enable staff to directly request the aid of specially trained individuals when a patient's clinical appearance is worsening.[22] The concept of the "rapid response team" was quickly adopted, with most hospitals in the US enacting at least some of the principles. Goals of the team are generally to prevent clinical deterioration, avoiding out-of-ICU intubation or cardiac arrest. Meta-analyses suggest that in that capacity, they have been successful, though whether they decrease overall mortality is unclear.[23-24] To date, no rapid response teams focused on AKI have been developed, though some small studies looking at early renal consult (within 24 hours) suggest some benefit.[3,25] To be able to provide true rapid response for AKI (i.e. within 30 minutes), an automated AKI detection system and a well-trained "Kidney Action Team" needs to be in place. We have pioneered the use of automated AKI alerts, and have a highly accurate electronic monitoring system in place across the study hospitals. In contrast to conventional rapid response teams, Kidney Action Teams can operate remotely, greatly expanding their reach and reducing associated costs. This may be of particular benefit in rural healthcare settings, where access to nephrology expertise is limited.

# 3 - Rationale/Significance

### 3.1 Problem Statement

It is unclear whether early, personalized recommendation for AKI diagnosis and treatment will meaningfully improve clinical outcomes among hospitalized patients.

### 3.2 Purpose of Study/Potential Impact

The purpose of this study is to evaluate the impact of a Kidney Action Team - a remote group of individuals who, by receiving real-time AKI alerts, can provide personalized initial recommendations for treatment and management. If the teams are shown to be successful, health systems may consider adopting this approach to mitigate the devastating downstream effects of AKI which include chronic kidney disease, dialysis, and death.

### 3.3 Potential Risks and Benefits

#### 3.3.1 Potential Risks

We consider the study to be minimal risk, as we are synthesizing information already available to providers in the medical record and offering recommendations for care that would already otherwise be available to the patient. These recommendations are not experimental, and represent best practices for AKI care. Potential risks are as follows:

- Inattention to AKI: A general risk of providing recommendations in a randomized fashion is the possibility that providers, who care for multiple patients each day regardless of randomization status, will become accustomed to receiving recommendations for their AKI patients and thus become inattentive to those patients in the control arm for whom they receive no recommendations. We will mitigate this effect by reminding providers in the recommendation note that this is part of a randomized trial and that recommendations are not sent for all patients who develop AKI. Pre-trial and periodic provider outreach will also be conducted to emphasize this point.
- Overtreatment: If the delivery of personalized recommendations affects physician behavior, then patients randomized to the intervention arm may be more likely to undergo certain tests or interventions, such as additional testing, than those in the control arm. While these interventions fall into the standard of care, the recommendations are made by a Kidney Action Team without direct patient interaction. Therefore, it is possible that some interventions may not be appropriate, may not benefit the patient, and may incur additional costs to the patient. We will make clear in the Kidney Action Team note that none of the recommendations are mandated, and that the providers clinical decisions should be paramount to any recommendation. Treating physicians are to use their own clinical judgement when making clinical decisions about these interventinos.
- Undertreatment/lack of follow up: Patients randomized to the intervention group may, based on recommendations, have certain kidney-toxic medications discontinued. It is possible that in some unique situations, discontinuation of medication may engender more risk (for example, discontinuation of a proton pump inhibitor in a

patient at high risk for gastrointestinal bleeding). Further, it may be incorrectly assumed by the primary care teams that the Kidney Action Team will follow up with further recommendations or with test results, and thus not follow up themselves. We will attempt to prevent this through our pre-trial and periodic educational efforts where we will remind primary providers of the nature of the trial, that it is still best to use their own clinical judgement when deciding to follow recommendations, and that recommendations only occur once, with no follow up from the Kidney Action Team. This will also be made clear in the Kidney Action Team note, which will indicate that the KAT will not follow-up on results of tests, and if more assistance is needed a formal renal consult should be called.

- As with all studies where PHI is collected, loss of privacy is at risk for subjects. We will limit this risk through our use of an entirely electronic data collection system and our data security plan. To minimize loss of privacy to subjects, all patient data will be kept on a secure, HIPAA-compliant server with 2-factor authentication, accessible only from within the Yale firewall, or via VPN protocols, and only by study personnel. In addition, at the time of data acquisition, a unique study ID number will be assigned to each patient. All PHI will be linked to this study ID number in a database that is separate and distinct from the primary dataset which includes clinical information. This linking dataset will be maintained on a separate HIPAA-compliant server and will only be accessible by the study investigators.

### 3.3.2 Potential Benefits

Subjects may directly benefit from participation in the study because their care teams may be more acutely aware of their medical condition and may provide more personalized, attentive care based on recommendations delivered from the Kidney Action Team. Should our paradigm of personalized treatment plans prove successful in improving patient outcomes, a broader implementation could provide benefits to society at large.

# 4 - Study Objectives

### 4.1 Hypothesis

A composite of progression of AKI, dialysis, and death will be significantly lower among patients randomized to receive Kidney Action Team recommendations compared to those randomized to usual care.

### 4.2 Primary Objective

This is a clinical trial designed to determine whether personalized recommendations for the workup and treatment of patients with Acute Kidney Injury (AKI) will improve the rates of AKI best practices and reduce the rates of inpatient dialysis, inpatient mortality and AKI progression in a hospitalized population.

# 5 - Study Design

### 5.1 General Design Description

This is a randomized, controlled, multicenter clinical trial to determine the efficacy of the delivery of personalized recommendations for the treatment of AKI in reducing clinical outcomes of AKI progression, dialysis, and death in hospitalized patients. Patients who develop AKI will be identified in real time and randomized to either usual care or to the active intervention group, in which the primary care team receives individualized recommendations for AKI treatment from a trained Kidney Action Team.

#### 5.1.1 Study Date Range and Duration

We anticipate approximately 36 months in which patients are randomized and data is collected, followed by 6 months of data analysis activities and publication. The entire study will take place over the course of 4 years.

#### 5.1.2 Number of Study Sites

The study will occur across two study sites.

1) The Yale New Haven Health System, comprising five hospitals in Connecticut and Rhode Island

2) Two hospitals within the Johns Hopkins University Hospital System: Johns Hopkins Medical Center and Johns Hopkins Bayview.

### 5.2 Outcome Variables

#### 5.2.1 Primary Outcome Variables

Composite of progression of AKI, dialysis, and death at 14 days post randomization or at hospital discharge. Progression of AKI is defined as a higher KDIGO-creatinine stage than that present at the time of randomization. Dialysis is defined by the receipt of hemodialysis, continuous renal replacement therapy, or peritoneal dialysis. Isolated ultrafiltration treatments for the purpose of volume removal will not be included.

#### 5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Several secondary outcomes will be assessed as follows:

-Inpatient mortality rate within 14 days

-Inpatient dialysis rate within 14 days

-Inpatient progression of AKI within 14 days

-The percent of discrete recommendations followed within 24 hours of randomization

-The rate of kidney consults within 14 days

-Rates of discharge to hospice care

-All documentation of clinical care related to the study, including procedures performed, medications administered, and laboratory tests ordered during hospitalization

We will also perform an assessment of heterogeneity of treatment affect across the study sites, as it is possible that the benefit of the KAT depends not only on patient characteristics, but upon local resources and practices.

### 5.3 Study Population

We will enroll adult inpatients in the Yale New Haven Health System and Johns Hopkins University Health System who develop Stage 1 AKI based on KDIGO creatinine criteria and who meet all inclusion and exclusion criteria described below.

Yale health system hospitals include Yale New Haven Hospital, Bridgeport Hospital, Greenwich Hospital, Lawrence and Memorial Hospital, and Westerly Hospital. Johns Hopkins sites include Johns Hopkins University Hospital and Johns Hopkins Bayview Campus. Sites will use a central IRB (BRANY).

#### 5.3.1 Number of Participants

We determined the overall sample size of this study based on the clinical composite outcome of progression of AKI, Dialysis, and Death. The baseline rate of this outcome is 21% based upon our preliminary data, and we felt that a relative 20% improvement (to 16.8%) would represent a clinically meaningful difference. In order to have 90% power to detect such a difference (or greater) if it exists at an alpha of 0.05, we would need to enroll 1,824 patients in each group, for a total of 3,648 in the study. Given concerns about contamination across the study arms (see III.J.9), we have increased this recruitment target by approximately 10% to a total of 4000 individuals. Enrollment of 4000 individuals will also allow us to detect a difference in the rate of adherence to recommendations of 10% of one standard deviation at an alpha of 0.05, which is ample power to determine if the provision of these recommendations change provider behavior.

#### 5.3.2 Eligibility Criteria/Vulnerable Populations

Adult inpatients within the Yale New Haven Health System who meet the following criteria:

*Inclusion Criteria:*

1. Adults ≥ 18 years admitted to a participating hospital
2. Stage 1 Acute Kidney Injury as defined by KDIGO creatinine criteria:
    a. 0.3 mg/dl increase in inpatient serum creatine over 48 hours OR
    b. 50% relative increase in inpatient serum creatinine over 168 hours

*Exclusion Criteria:*

1. Admission to hospice service or comfort measures only order
2. Recipient of a solid organ transplant
3. Immediate dialytic indication determined by the following:
    a. K ≥7 meq/L
    b. Acute ingestion of dialyzable toxin

   c. Refractory volume overload
   d. BUN > 150 mg/dL
   e. pH < 7.15 despite ventilatory support
4. Pre-existing CKD stage V or ESRD
5. Initial hospital creatinine > 4.0 mg/dl
6. Nephrology already consulted
7. Status post nephrectomy (partial or radical) during index admission

# 6 - Methods

### 6.1 Treatment - Device

#### 6.1.1 Intended use for the device

*Kidney Action Team Recommendations*

Dedicated and trained Kidney Action Teams (KATs) will each consist of an advanced practitioner and a pharmacist and will be supervised by a nephrologist. KATs will be available 24 hours a day, 7 days a week, barring extenuating circumstances. The KAT will be notified, in real-time, of all randomized patients at their site who meet enrollment criteria via an automated electronic health record system. The KAT will be tasked with providing individualized recommendations for AKI workup and treatment based on best practices identified within several kidney domains. Recommendations will be created for each randomized patient, however, they will only be delivered to the primary care teams of those patients who have been randomized to the active intervention group. This strategy allows for both the blinding of the KAT as well as a comparison in the proportion of recommendations implemented between the control and intervention groups. Recommendations for those in the intervention group will be made and delivered within one hour of AKI alert via a specialized note (Appendix 1) that is entered into the patient's chart and flagged for cosigning by the covering primary physician (i.e., the person signed on to EPIC as the patient’s covering provider for that shift).

We have designed the recommendations to be limited to specific domains of AKI diagnosis and treatment in order to minimize the variability in recommendations across members of the Kidney Action Teams and to allow for timely recommendations to be made. These domains include potassium management, acid/base management, fluid management, drug redosing and cessation, and diagnostic work-up. We have also included a set of universal recommendations that will be delivered to all patients randomized to the intervention group, as we feel these to be a necessary component of a standard work-up for any AKI patient.

Universal AKI recommendations will be recommended if not yet performed in the 48 hours prior to randomization and include:

- Obtaining a urinalysis
- Obtaining a urine sodium, potassium, chloride, creatinine measurement
- Obtaining a post-void residual measurement or renal ultrasound to rule out obstruction
- Avoiding new nephrotoxic exposures
- Measuring serum creatinine at least every 24 hours during the inpatient stay
- Strict measurement of fluid input and output

Recommendations in the other domains will be personalized and may include the following:

*Potential Recommendations for Potassium Management*

- No recommendation
- Administer loop diuretic:
    - Furosemide 40mg IV x 1 dose
    - Furosemide 60mg IV x 1 dose
    - Furosemide 80mg IV x 1 dose
    - Furosemide 120mg IV x 1 dose
    - Furosemide 160mg IV x 1 dose
    - Administer metolazone 30 minutes prior to loop diuretic
- Other (specify)Low (2g) potassium diet
- Potassium binder (such as sodium polystyrene sulfate, patiromer, or sodium zirconium cyclosilicate)
- Lactated Ringer Bolus of 500ml
- Recheck potassium within 6 hours
- Recheck potassium within 2 hours
- Calcium Gluconate 9meq IV
- Insulin 5 units IV, with or without 50% dextrose
- Insulin 10 units IV, with or without 50% dextrose (1 amp IV)
- Nephrology Consult
- Telemetry Monitoring
- Other (specify)

*Potential Recommendations for Acid/Base Management*

- No recommendation
- Order ABG or VBG
- Check toxic alcohols
- Check lactate, beta-hydroxybutyrate
- Give 1L of isotonic sodium bicarbonate
- Start oral sodium bicarbonate (specify dose)
- Other (specify)

*Potential Recommendations for Diagnostic Testing*

- No recommendation
- Order urinalysis

- Order CK, Haptoglobin and LDH
- Consider renal consult
- Other (specify)

*Potential Recommendations for Fluid Management*

- No recommendation
- 1L Ringer's lactate bolus
- Albumin 25g x 1
- Albumin 50g x 1
- Caution with IV fluids if concern for respiratory compromise
- Check orthostatic vitals
- Re-assess volume status prior to further volume resuscitation
- Avoid IV fluids
- Obtain chest x-ray
- Obtain transthoracic echocardiogram
- Other (specify)

*Potential recommendations for medication management:*

- No medications to stop or dose adjust
- Stop NSAID
- Stop ACEi/ARB/mineralocorticoid antagonist/Renin Inhibitor
- Stop Proton Pump Inhibitor
- Stop other nephrotoxic medication (specify)
- Adjust the dose of this medication (specify)

Monitor the level of this medication (specify)Recommendations will only be made once for each patient (within one hour of AKI onset) and with no follow-up on results from these recommendations. We will clearly communicate this with all exposed physicians during our educational outreach. This ensures no post-randomization unblinding and will also increase generalizability by decreasing the burden on the Kidney Action Teams.

### 6.1.2 Device administration and schedule

The Kidney Action Team will provide personalized recommendations within 1 hour of the AKI alert being generated. This will be the sole interaction between the KAT and the study patient. No follow-up of recommendations will be performed.

### 6.1.3 Method of Assignment/Randomization

Randomization will be performed within REDCap using a computer-generated randomization table which will use permuted blocks (of 4, 6 and 8 individuals). Randomization will be stratified by study hospital.

The Kidney Action Team will create recommendations for all patients that meet eligibility criteria, regardless of randomization status, which will preserve their blinding. (Recommendations will only be delivered to patients in the intervention group). Providers and patients will not be blinded. Study investigators and analysts will be blinded to randomization status.

### 6.1.4 Concomitant therapy

There are no restrictions on concomitant therapy in this trial.

## 6.2 Assessments

### 6.2.1 Safety/Pregnancy-related policy

Pregnant women and those who are of child-bearing age are not excluded from this study.

## 6.3 Study Procedures

### 6.3.1 Informed Consent

Due to the nature of the study, it is not feasible to consent subjects, as it would severely contaminate the exposure of interest. For example, a control subject who was sought out for consent might indicate to his/her provider that they were enrolled into the study and would reveal their AKI diagnosis. Further, it would be infeasible to consent patients in a timely manner (at the onset of AKI) that is needed for quick delivery of recommendations to the primary care team. To avoid these issues, we could obtain informed consent from every patient on admission to the hospital. However, given the incidence of AKI is approximately 15% of admissions, this would be impractical as well as unnecessary for the vast majority of patients, exposing roughly 85% of patients never deemed eligible for the trial to the risks of loss of confidentiality present in all research with human subjects. Given that the proposed research presents no more than minimal risk to subjects and that no procedures are being performed that require consent outside of the research paradigm, we request a waiver of informed consent for this study. Waiver of consent and HIPAA authorization from the BRANY IRB for all sites, including JHU and YNHH hospitals under their own potential IRB.

### 6.3.2 Screening

Screening of potential participants will be completed by an electronic AKI "sniffer" algorithm, already in place at the study hospitals. The algorithm will flag patients with AKI as defined in the inclusion criteria, and evaluate whether inclusion / exclusion criteria are met. The patient information will then be passed, in real time, to the Kidney Action Team who will assess eligibility for enrollment into this trial. The KAT will be able to complete a brief screening assessment prior to their formal evaluation to ensure that the patient is truly eligible as well.

### 6.3.3 Recruitment, Enrollment and Retention

As this study will be conducted under a waiver of informed consent, recruitment is automatic. We do note that the study hospitals have an "opt out" option for research that uses the electronic health record. These patients will not be enrolled in this study.

Patients will be followed electronically throughout their hospitalization. There are no formal study visits.

#### 6.3.4 On Study Visits

There are no formal study visits.

#### 6.3.5 End of Study and Follow-up

Follow-up will conclude at the time of discharge from the hospitalization in which the patient was randomized.

### 6.4 Statistical Method

#### 6.4.1 Statistical Design

We will compare rates of the primary outcome of progression of AKI, dialysis and death using the Cochrane-Mantel-Haenszel chi-square test, accounting for stratification by hospital. We will average proportion of recommendations followed within 24 hours between the intervention and control group using the Van Elteren test to account for stratification by hospital.

#### 6.4.2 Sample Size Considerations

We determined the overall sample size of this study based on the clinical composite outcome of progression of AKI, Dialysis, and Death. The baseline rate of this outcome is 21% based upon our preliminary data, and we felt that a relative 20% improvement (to 16.8%) would represent a clinically meaningful difference. In order to have 90% power to detect such a difference (or greater) at an alpha of 0.05, we would need to enroll 1,824 patients in each group, for a total of 3,648 in the study. Given concerns about contamination across the study arms (see III.L.9), we have increased this recruitment target by approximately 10% to a total of 4000 individuals. Table 2 shows a breakdown of recruitment by study site. Given the fact that this trial will operate under a waiver of informed consent, and our prior track record in this space, we expect full accrual across both sites within 3 years. Enrollment of 4000 individuals will also allow us to detect a difference in the rate of adherence to recommendations of 10% of one standard deviation at an alpha of 0.05, which is ample power to determine if the provision of these recommendations change provider behavior.

#### 6.4.3 Planned Analyses

##### 6.4.3.1 Primary Analyses

The primary analysis will compare the proportion of patients experiencing the primary outcome (progression of AKI, Dialysis, or Death) at 14 days after randomization. We will compare the difference using the Cochrane-Mantel_Haenszel chi-square test, accounting for stratification by study hospital.

##### 6.4.3.2 Analysis of Subject Characteristics

We will compare the baseline characteristics of subjects in the two study groups using chi-square tests (for categorical variables) and Wilcoxon Rank Sum tests (for continuous variables).

# 7 - Trial Administration

### 7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

The study will be conducted under a waiver of informed consent.

Due to the nature of the study, it is not feasible to consent subjects, as it would severely contaminate the exposure of interest. For example, a control subject who was sought out for consent might indicate to his/her provider that they were enrolled into the study and may subsequently affect provider behavior. Further, it would be infeasible to consent patients in a timely manner, at the onset of AKI, that is required for rapid delivery of recommendations to the primary care team. To avoid these issues, we could obtain informed consent from every patient on admission to the hospital. However, given the incidence of AKI is approximately 15% of admissions, this would be impractical as well as unnecessary for the vast majority of patients, exposing roughly 85% of patients never deemed eligible for the trial to the risks of loss of confidentiality present in all research with human subjects. Given that the proposed research presents no more than minimal risk to subjects and that no procedures are being performed that require consent outside of the research paradigm, we request a waiver of informed consent from the IRB.

Subjects will not be informed of their participation in the trial at a later date. Informing patients to the presence of AKI, which may be unfamiliar to most, may engender significant stress without offering any tangible benefit or guideline-based follow-up or intervention to pursue. Patients may also incorrectly assume that AKI is an iatrogenic condition caused by poor medical care, or that they were not receiving the full extent of medical care available in the absence of the recommendations when assigned to the control group. However, our study is simply synthesizing already available data from the electronic medical record and recommending a plan of care that is already available for physicians to utilize. We will, however, update all clinicians with the results after trial completion. While no data will be linked to any specific provider, we will be able to relay broader generalizations (e.g. personalized recommendations decrease the use of certain nephrotoxins).

### 7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation as well as appropriate submission to the FDA.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year. A study closure report will be submitted to the IRB after all research activities have been completed. Other study events (e.g. data breaches, protocol deviations) will be submitted per the IRB's policies.

### 7.3 Subject Confidentiality

Data collected in the course of the study will be de-identified and stored on REDCap and on a secure HIPAA-compliant central server within the Clinical and Translational Research

Accelerator. The server is only accessible from within the Yale intranet (or via VPN remotely) and additionally requires separate logon username and password. No PHI will be included in analysis or publication. All analyses will proceed on this server alone.

We will maintain a linking file in a separate location that will allow for future linking of de-identified data to protected health information (PHI) for the purpose of potential future studies. Studies that require the use of PHI (for example, linking patient info to national outcomes databases) will require approval the investigators.

### 7.4 Deviations/Unanticipated Problems

If the study team or monitor becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported by the Investigator to the reviewing IRB according to their requirements and to the Sponsor within 10 business days. Within 10 business days of the receipt of this information, the Sponsor will notify in writing other reviewing IRBs, the study monitor (if not already involved), and the FDA in accordance with applicable regulations. Protocol deviations will be identified through the review of the CRFs and collected data by the Sponsor-Investigator after each subject is enrolled. The Sponsor-Investigator will also have a formal discussion with the study investigator after each case to assess for any potential protocol deviation. The study Monitor will also review each case and assess for protocol deviations.

### 7.5 Data Collection

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the investigators electronically (e.g., laboratory data). The investigators are responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

  Data will be obtained from the electronic health record via Yale's Joint Data Analytics Team (JDAT) as raw flat files from Clarity, the relational database from Epic. These files will then be transferred to our server via secure FTP. A deidentified dataset will be constructed by the study team using the Safe Harbor method of the HIPAA Privacy Rule, namely the removal of all 18 HIPAA identifiers.

  Non PHI elements of this data pull will include the following (looking back a minimum of 10 years):

  - Full patient medical history
  - All available clinical care information during index encounter
  - All available information from follow-up encounters following index hospitalization
  - Provider type/class and location of treatment for all follow-up encounters following index hospitalization
  - Patient coverage status

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The investigators are responsible for the data management of this study including quality checking of the data.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for five years after study completion unless local regulations or institutional policies require a longer retention period.

### 7.6 Access to Source

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 7.7 Data or Specimen Storage/Security

No specimens will be collected in the course of this study. Data Protection

- Participants will be assigned a unique identifier by the investigators.

### 7.8 Retention of Records

Records will be retained for at least 5 years after the end of the study.

### 7.9 Study Monitoring

The study will be monitored by the internal team as well as a dedicated external Data and Safety Monitoring Board.

The DSMB will meet at least twice a year to review data and will have a formal meeting to assess the interim analysis results.

### 7.10 Data Safety Monitoring Plan

Data and Safety Monitoring Board

- Participant safety will be continuously monitored by the external DSMB, which includes safety signal detection at any time during the study
- Case unblinding may be performed for above reviews if necessary.

The DSMB may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

### 7.11 Study Modification

Study modifications will be implemented upon approval from the IRB.

### 7.12 Funding Source

This study is funded by a grant from the Association of Healthcare Research and Quality.

### 7.13 Publication Plan

- The results of this study may be published or presented at scientific meetings.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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**Appendix 1: Kidney Action Team Note Template**

**Kidney Action Team Recommendation Note**

Date: Time:

The Kidney Action Team is a group of clinicians designed to provide personalized recommendations for the diagnosis and treatment of patients with Acute Kidney Injury (AKI).

We have been notified that this patient has developed AKI within the past hour. We have reviewed the patient's chart and, based on the patient's current status and medical history, make the specific recommendations listed below.

*****For all AKI patients, we recommend continued follow-up of serum creatinine and avoiding nephrotoxic exposures.*****

**KIDNEY ACTION TEAM PERSONALIZED RECOMMENDATIONS FOR YOUR AKI PATIENT:**

- **Obtain urinalysis (if not already obtained)**
- **Avoid new nephrotoxic exposures**
- **Follow creatinine at least every 24 hours**
- **Rule out obstruction via PVR or ultrasound**
- **Provide bicarbonate supplementation**
- **Stop PPI**
- **Consider Renal Consult**

**Please note:** This patient is part of a randomized clinical trial designed to test the efficacy of personalized recommendations for the diagnosis and treatment of Acute Kidney Injury. You will NOT receive this recommendation note for all patients who develop AKI.

The Kidney Action Team has not seen or examined this patient. Our recommendations are based on chart review only. **It is your choice to follow these recommendations using your own clinical judgement and your examination of the patient and his/her medical history.** Should you choose to follow any of the recommendations, the Kidney Action Team will not follow up on test results or provide any further recommendations. *If you need assistance with AKI management, please consider a formal kidney consult. Medication recommendations are based on currently prescribed medications. Please reach out to your floor pharmacist if any further questions about starting renally cleared medications.*

Please cosign to acknowledge receipt of the recommendations.

Signed By:

Date: