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Electronic **A**lerts for Acute Kidney **I**njury **A**melioration **(ELAIA-1):** A Completely Electronic, Multi-Center, Randomized Controlled Trial: Design and Rationale

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Abstract:

Introduction: Acute kidney injury (AKI) is common among hospitalized patients and under-recognized by providers yet carries a significant risk of morbidity and mortality. Electronic alerts for AKI have become more common despite a lack of strong evidence of their benefits. We designed a multicenter, randomized, controlled trial to evaluate the effectiveness of AKI alerts. Our aim is to highlight several challenges faced in the design of this trial, which utilizes electronic screening, enrollment, randomization, intervention, and data collection.

Methods and analysis: The design and implementation of an electronic alert system for AKI was a reiterative process involving several challenges and limitations set by the confines of the electronic medical record system. The trial will electronically identify and randomize 6,030 adults with AKI at 6 hospitals over a 1.5 – 2 year period to usual care versus an electronic alert containing an AKI-specific order set. Our primary outcome will be a composite of AKI progression, inpatient dialysis and inpatient death within 14 days of randomization. During a one-month pilot in the medical intensive care unit of Yale New Haven Hospital**,** we have demonstrated feasibility of automating enrollment and data collection. Feedback from providers exposed to the alerts was used to continually improve alert clarity, user friendliness, and alert specificity through refined inclusion and exclusion criteria.

Ethics and dissemination: Our study qualified for a waiver of informed consent as it presents no more than minimal risk and cannot be feasibly conducted in the absence of a waiver. We are committed to open dissemination of our data through clinicaltrials.gov and submission of results

to the NIH data sharing repository. We hope that completion of our trials will contribute to the continued improvement of patient outcomes.

Trial Registration: clinicaltrial.gov NCT02753751

Keywords: Acute kidney injury, acute renal failure, electronic health record, randomized, alert, clinical decision support

Article Summary:

This manuscript discusses the design, ethical framework, and plan of execution of a multicenter randomized controlled trial of electronic acute kidney injury alerts.

Strengths and Limitations of this Study:

- A multicenter, randomized controlled trial which is the first of its kind to rigorously test the efficacy of an electronic alert at multiple hospitals before broad implementation.
- Carefully designed selection criteria to reduce the rate of false positives.
- Complete reliance on the electronic medical record for subject screening, enrollment, and randomization and delivery of the intervention, which reduces cost and increases scope of data collection, efficiency and generalizability.
- Reliance on the electronic medical record presents limitations in alert design and randomization methods.

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function, which results in the accumulation of metabolic waste products, as well as dysregulation of volume status, electrolyte and acid-base balance. This condition is common, estimated to occur in about 5-20% of all hospitalized patients, and carries a significant, independent risk of mortality of up to 20% in some studies.[1-3]

International guidelines for the treatment of AKI focus on appropriate management of drug dosing, avoiding nephrotoxic exposures, and careful attention to fluid and electrolyte balance.[2] Early nephrologist involvement may also improve outcomes in the care of acute kidney injury.[3] Without appropriate provider recognition of AKI, however, none of these measures can be taken, and patient outcomes may suffer. Unfortunately, AKI (which is asymptomatic) is frequently overlooked by clinicians and carries a substantial cost, morbidity, and mortality burden.[1] In a prior study at a tertiary care academic hospital, we found that only 43% of patients had documentation of AKI in the medical record and that AKI documentation was associated with decreased mortality, adjusted for admission type and severity of illness.[4] Further, patients with AKI often continue to be exposed to kidney-toxic medications.[5,6]

Automated alert systems have emerged as a strategy to influence clinician detection of specific clinical states and subsequent behavior. Several randomized trials have demonstrated the efficacy

of using alerts, particularly in minimizing drug interactions in hospital settings.[7-11] In 2014, our group was the first to conduct a pilot, randomized trial of electronic alerts for acute kidney injury.[12] The trial, which randomized 2373 patients with AKI, found that alerting a single physician to the presence of AKI did not improve the course of AKI or reduce dialysis or death rates. Our pilot study demonstrated that there is clinical equipoise regarding the effectiveness of alerting, and that alerting to the presence of this condition should not be considered standard of care.

However, our pilot study had several limitations which we address in a new randomized trial. The prior study was conducted in a single hospital, and the alert itself did not describe specific actions that a provider could take in response to the alert. The alert was delivered only once, to a single provider (and a unit pharmacist) without contextualization (i.e., it occurred outside of the relevant electronic health record). In the present trial, we expand upon our prior study to determine if the use of an electronic alert system will improve best practices in regards to care of hospitalized patients with acute kidney injury and/or improve rates of progression of AKI, dialysis, or death in hospitalized patients. This trial is notable for its reliance on the EHR to screen, enroll, randomize, and deliver the intervention to patients. It further differs from our pilot study in that alerts are integrated at the point of care, that they are delivered to multiple providers, and in its use of a multicenter design which allows for assessment of heterogeneity of alert effect across different hospital types with diverse patient populations.

METHODS AND ANALYSIS

The study design was approved by the Yale Institutional Review Board (Yale IRB# 1604017596) and is registered under clinicaltrials.gov NCT02753751. It operates under a waiver of informed consent (see *ethics* section). The protocol conforms to the principles of the Declaration of Helsinki and the full study protocol is accessible at www.akistudy.org. This manuscript was submitted using the SPIRIT reporting guidelines.[13]

This is a multi-center, parallel-group, randomized, controlled trial to evaluate the efficacy of an AKI alert system for hospitalized patients with acute kidney injury. The six participating centers are described in Table 1 and were selected on the basis of their shared use of an electronic health record (Epic Systems, Verona WI). The trial began on March 26th, 2018 and is expected to enroll patients for 1.5 to 2 years.

Table 1: Participating centers in the ELAIA-1 trial

INSTITUTION	LOCATION	TYPE	TEACHING	BEDS
Bridgeport Hospital	Bridgeport, CT	Community	Yes	383
Greenwich Hospital	Greenwich, CT	Community	Yes	206
The Hospital of St. Raphael	New Haven, CT	Community	Yes	511
Lawrence and Memorial Hospital	New London, CT	General/acute care	No	280
Yale New Haven Hospital	New Haven, CT	Acute/Tertiary	Yes	1,030
Westerly Hospital	Westerly, RI	Community	No	60

Participants

All inpatients 18 years of age or older at the six participating centers who develop AKI will be automatically enrolled into the trial. AKI is defined as an increase in serum creatinine concentration of 0.3 mg/dL within 48 hours or a relative increase of 50% within 7 days in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[2]

Exclusion criteria

Our exclusion criteria are designed to reduce the rate of "false-positive" alerting (alerts sent for individuals without true AKI). Patients with initiation of dialysis prior to AKI onset and with an end-stage kidney disease (ESKD) diagnosis code will be excluded. Patients with an initial serum creatinine ≥ 4.0mg/dL will also be excluded due to a lack of consensus definitions of AKI in this population. Patients admitted to hospice services or who are made "comfort measures only" will also be excluded, as the use of an electronic alert is not expected to impact their care. We will also exclude patients within 6-months of kidney transplant, as these individuals are monitored closely for changes in kidney function when hospitalized.

Intervention

Patients will be randomized to either usual care (UC) or to the AKI electronic alert system (Alert). The alert consists of a “pop-up” generated within the EMR when the provider accesses a patient record (Figure 1). [Insert Figure 1.]

The electronic alert text was designed to inform providers of the presence of acute kidney injury in their patient, as well as provide a minimum and maximum creatinine value within the prior 7 days. Therefore, the language was kept broad and simple. The alert reads "Your patient has been identified as having acute kidney injury. Relevant creatinine values over the last seven days are listed below." The most recent creatinine value, as well as the lowest and highest values in the past 7 days, will be listed. This is followed by the following statement "THIS ALERT DOES NOT FIRE FOR ALL PATIENTS. This patient is part of a randomized trial. For more information, click here: www.akistudy.org." The electronic alert also includes a link to an AKI order set, which includes labs and imaging to further work-up acute kidney injury. The order set was designed so as not to promote or increase the use of any one particular therapeutic strategy, as this could vary from patient to patient. Finally, at the bottom of the alert, an option to either "agree" or "disagree" with the alert is provided.

In our previous study, only one primary in-house provider received an alert per patient, however we hypothesized that creating a more comprehensive alerting system may improve alert efficacy. Providers who will receive an alert include physicians, physician assistants (PAs), nurse practitioners (NPs) and advanced practice registered nurses (APRNs). Any of the above type of providers, regardless of relationship to the patient, will receive the alert when the patient's chart is opened. This population of providers was chosen as (unlike nurses, pharmacists, or medical students) they are able to enter and discontinue diagnostic and treatment orders that may impact the course of AKI.

Mode and invasiveness of alerting were important considerations of the present study. In our previous study, we used a text-based paging system for alerting providers to the presence of acute kidney injury. This was a minimally invasive approach that was disconnected with provider activity in the EMR. In this trial, the alert occurs at the point of care, and is linked to an AKI order set and evidence-based practice guidelines.

Alert frequency

The AKI alert will be displayed to the relevant provider whenever the patient's chart is opened while they have AKI. If the provider "dismisses" the alert, it will continue to "pop-up" on each subsequent opening of the patient's medical record by that provider. The alert will stop firing for the provider under the following conditions:

- The provider acknowledges the alert by "agreeing" that AKI is present, or by "disagreeing" that AKI is present with an accompanying explanation (alert will then be suppressed for 48 hours)
- The patient's most recent creatinine no longer meets criteria for AKI
- The patient receives an order for hemodialysis, continuous renal replacement therapy, or peritoneal dialysis
- The patient is transferred to the hospice service, is made comfort measures only, or dies
- The patient is discharged from the hospital

Though we recognize that repeated alerts may become onerous and lead to alert fatigue[14], we felt that physicians may not recognize the presence of acute kidney injury or fully read the alert if

only provided with one alert. In addition, we wanted to study the utility and usefulness of the AKI order set and/or use of the link for KDIGO clinical practice guidelines, which would be more likely to occur if providers view and read the alert multiple times. In order to counteract potential alert fatigue, we do give providers the option to suppress the alert, as stated above.

We are also aware that repeated alerting may lead to variable "dosing" of the intervention. Because our prior study involved one alert per patient, a uniform intervention was guaranteed for all patients in the alert arm. Here, it is feasible for patients to experience different "doses" of the alert, dependent upon the duration of AKI, frequency and timing of EMR access, and provider response to the alerts. As such, this trial is best conceptualized as an attempt to measure the effectiveness of an alert protocol rather than of an individual alert *per se*.

Randomization

Simple randomization is achieved within the Epic EMR system using an internal random number rule. Beyond the primary intervention, no further tests or procedures will be performed on subjects in this trial.

Though commonly used in clinical trials, a permuted block randomization method was not utilized as this EHR has neither the functionality to generate permuted block lists or to import external randomization lists. Allocation concealment is maintained as the alert process is completely automated and performed within the EHR. In addition, we chose not to randomize at the provider level because this was deemed infeasible; patients at the participating hospitals are

cared for by multiple providers, who may change during the course of a patient's hospital stay. Finally, cluster randomization was infeasible given the limited number of clusterable entities (i.e. six hospitals). Ward-based clustering would not be feasible given the fact that physicians (especially consultants) see patients throughout a given hospital. This has important implications with regards to contamination (see below).

Blinding

Participants and the study team will be blinded to the intervention, though obviously care providers will be aware of treatment assignment.

Clinician Outreach

While the unit of randomization is the patient, clinicians may also be considered subjects of this research. We will engage in pre-trial and periodic outreach to all clinicians who may be exposed to this study, informing them of the nature of the study, the fact that it is a randomized trial, and that alerts do not fire for all patients with AKI. We will additionally inform them that limited data is being collected regarding provider behavior. The alert pop-up contains methods to contact the study team. Most notable, if "disagree" is clicked, a free-text box is opened that allows providers to communicate their concern directly to the team. While piloting the popup in pre-trial activities, we used these responses to further tailor the language of the alert. We will also make it clear that data subject to clinician behavior (such as AKI documentation) will NOT be linked to individual clinicians.

Primary Outcome

The primary outcome will be a composite of progression to a higher stage of AKI, inpatient dialysis and inpatient death within 14 days of randomization. We chose this time frame for outcome assessment as the effect of an AKI alert might be diluted over time as more issues arise during the hospitalization.

Secondary outcomes of interest

Secondary outcomes of interest are listed in Table 2. Many of these are process measures, as we are particularly interested in measures that may change as a result of AKI alerts. In determining secondary outcomes of interest, we needed to balance outcomes that would be of interest to clinicians and other care providers with the feasibility of accurately determining those specific outcomes. This was particularly relevant for "best practices" such as dose-adjustment for medications, which can be somewhat subjective and thus requires direct chart review for determination.

To operationalize our "duration of AKI" endpoint, we define "C1" as the AKI-defining creatinine, and "C0" as the lowest preceding creatinine in the past 48 hours or past seven days depending on which KDIGO AKI criteria was met. For those defined by both, C0 will be the lower of the two creatinine values. Cessation of AKI will occur when a subsequent creatinine measure is within 0.3 mg/dl or 50% of C0, again depending on the KDIGO AKI criteria initially

met (and within both if both criteria were met). While C0 may not represent true "normal" kidney function for a patient, selecting this time point avoids imputation of a baseline while avoiding potentially artificially prolonged AKI duration. Further, as it is conceivable that patients can be discharged prior to recovery and receive no follow-up creatinine measurements, we will evaluate differences in duration of AKI through the use of Kaplan-Meier estimators, allowing for censoring at death or discharge.

Table 2: Secondary outcomes of interest

ENDPOINT AND DEFINITIONS	DATA SOURCE
Mortality outcomes	
Inpatient mortality	Hospital record
Dialysis outcomes	
Inpatient dialysis	Order entry system
Discharged on dialysis	Social work records
Renal Failure Outcomes	
Percent who progress to Stage 2 AKI	Laboratory values
Percent who progress to Stage 3 AKI	Laboratory values
Duration of AKI	Laboratory values
Readmission Rate and Costs	
30-day readmission rate	Hospital record
Cost of index hospitalization	Billing records
Individual "Best Practice" Outcomes (proportion achieved per patient in study	

arm during index hospitalization)	
Contrast administration	Order entry system
Fluid administration	Order entry system
Aminoglycoside administration	Order entry system
NSAID administration/cessation	Order entry system
ACE inhibitor administration/cessation	Order entry system
Urinalysis order	Order entry system
Documentation of AKI	Post-discharge ICD-10 codes
Monitoring of creatinine	Order entry system
Monitoring of urine output	Hospital Record
Renal consult	Direct chart review
Provider awareness outcomes	
Chart documentation of AKI (by post-discharge ICD-10 codes)	Billing records
Chart documentation of AKI (adjudicated)	Direct chart review

AKI: acute kidney injury; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin converting enzyme

Subgroup analysis

The effect of the alert may differ based on several patient characteristics. We have therefore pre-specified several sub-groups of interest that are outlined in Table 3 and that will be considered

hypothesis-generating for the future design of targeted alerts towards populations that are more likely to benefit from an alert system. Additionally, because we are enrolling patients across six hospitals that vary in size, type, and patient population, we will perform an exploratory analysis to determine the efficacy of alerts independently at each site.

Table 3: Planned subgroup analyses and justification

Subgroup of primary interest	**Justification**
Surgical patients (defined by admission to a surgical team)	Risk of under-documentation (reference)
Subjects with baseline creatinine <1.0mg/dl	AKI occurs when creatinine in "normal range"
Subjects with baseline creatinine <0.5mg/dl	AKI occurs when creatinine in "normal range"
Females	Lower rate of creatinine increase after AKI (reference)
African Americans	Higher rate of creatinine increase after AKI (reference)
Elderly (age >65, age >70 and age >75)	Lower rate of creatinine increase after AKI (reference)
Subjects in an ICU at the time of the alert	AKI may be overlooked in the setting of multiple clinical problems
Subjects who enter the study based on a 50% increase in creatinine vs. a 0.3mg/dl increase	Clinicians may be less likely to recognize a 0.3mg/dL change vs a 50% change

in creatinine vs both

Contamination

As providers are not randomized and will be aware of patients who are randomized to the experimental arm, there is a risk of contamination of the intervention. Providers may use the information provided in the AKI alert (i.e. definition of AKI, best practices with respect to AKI care, etc.) to improve their ability to detect AKI in patients not randomized to the experimental arm. In addition, improved knowledge with respect to the definition of an acute kidney injury and its appropriate management may improve the ability to detect AKI over time. In order to address this issue, we will examine the outcome rate in the control arm over time; if the outcome rate in the control arm improves over time, this may suggest contamination.

Beyond that, we have a pre-trial baseline cohort of patients that would be enrolled were the trial actively recruiting. While temporal shifts in treatment may change outcomes over time independent of alerting, a significant improvement in AKI outcomes in the control arm of the trial vs. the pre-trial cohort would further suggest contamination.

Finally, it is possible that providers exposed to alerts may actually be at risk of increased *inattention* to AKI in patients of the control arm, as they may become accustomed or dependent upon receiving an alert as recognition of AKI. We will attempt to mitigate this through periodic

outreach to clinicians and explicitly stating on the alert that not all patients with AKI trigger an alert.

Statistical Analysis

The primary analysis will utilize the intention to treat principle. The proportion of patients who experience the primary outcome in the intervention and control groups will be compared by the chi-square test with Mantel-Haenszel correction for the 6 study strata (by hospital). Statistical significance will be based on a two-sided p-value of <0.05.

Power and sample size considerations

To estimate the sample size, we conducted a retrospective analysis of patients with AKI at 3 of the 6 study hospitals. The composite outcome of progression of AKI, dialysis, or death occurred in 24.5% of 29,027 individuals with AKI in this analysis. A 20% reduction in this proportion (to 19.6%) would be clinically meaningful. To that end, a sample size of 2512 in each arm achieves 90% power to detect a difference this large at a two-sided alpha of 0.05 as calculated using the Cochran-Mantel-Haenszel test (accounting for 6 hospital strata). This gives a total population of 5,025 individuals with AKI. We have elected to increase this number by 20% to account for potential contamination of the effect across study arms, leading to a final sample size of 6,030 individuals.[15] In addition to adequately powering for the primary clinical outcome, this sample size will allow us to detect at least a 16% increase in the odds of more best practices being completed in the intervention group.

Interim Analysis

We plan to have one interim analysis at the mid-point of the trial when 50% of patients have been enrolled. The interim analysis will allow us to alter the sample size or stop the trial earlier for ethical considerations, unexpected adverse events or high efficacy. The trial will stop for declaring efficacy if the effect size is large. We will use the O'Brien and Fleming stopping rule to stop the trial at a p-value of 0.001 for efficacy.[16] Alerting harm will be also be assessed using the primary outcome, but the threshold for stopping the study will be greater, at a p-value of 0.005. The DSMB will be unblinded to the study outcomes for these assessments, but the study team will remain blinded throughout.

Pre-intervention data

Pilot in the Medical Intensive Care Unit (MICU)

Prior to the implementation of the electronic alert across all six hospital systems, we piloted the alert from 01/08/2018 to 02/08/2018 in the medical intensive care unit at Yale-Haven Hospital. The purpose of this pilot phase was to evaluate the appropriateness of alerting, to solicit feedback from providers, and to ensure that the electronic methods of data capture were valid. There were 77 patients randomized (37 to alert, and 40 to control). The alert fired a total of 2,355 times, a median (IQR) of 48 (23- 89) alerts per patient. Of 509 providers eligible to receive alerts, 323 providers received at least one, a median of 1 (0 – 9) alerts per eligible provider (Figure 2). The

maximum number of alerts received by a single provider over the 30 days of the pilot was 78. That provider was an acute care nurse practitioner assigned to the MICU for the duration of the pilot. [Insert Figure 2.]

Outcomes for all randomized patients were as expected for a medical intensive care unit population. Inpatient death occurred in 29 (37%) of patients, while 4 (5.1%) were discharged home. The remainder of patients were discharged to a nursing facility, hospice, or transferred to another medical facility. In terms of AKI outcomes, the majority of these patients (52%) never had progression of AKI, 29% progressed to stage 2, and 18% progressed to stage 3.

Several iterations to the alert were made over the course of the pilot in response to provider feedback and internal testing. These are summarized in Box 1:

Change	Motivation
Excluded patients with "deceased" status	Occasional alerting on patients who had recently died was ghoulish and unactionable
Modified language to make it clear that "agreeing" with alert suppresses future alerts for themselves only	Providers are eager to find ways to suppress alerts once they have been alerted
Extended the "prior dialysis" exclusion criterion to one year	Some chronic dialysis patients would initially lead to an alert
Excluded providers who cannot enter orders	AKI Order set is not useful for individuals (such as nurses, medical students) who are unauthorized to enter orders.

Box 1: Summary of changes made to alerting during the piloting of the alert system.

ETHICS AND DISSEMINATION

Ethical Issues

This study posed several ethical issues that are worthy of discussion. First, in order to efficiently proceed with the study, we obtained a waiver of informed consent. United States federal guidelines require that in order to obtain a waiver of consent, 1) the research pose no more than minimal risk to the subject, 2) the waiver not adversely affect the rights and welfare of the subject, 3) the research could not be practicably carried out without a waiver and 4) whenever appropriate, the subjects be provided with additional pertinent information after participation. We felt that our study met all of the criteria noted above to qualify for a waiver of informed consent.

Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. We do not feel that post-facto informing of patients randomized in this trial is appropriate for several reasons. First, there is no guideline-based specific follow-up or intervention for acute kidney injury. Second, many patients may incorrectly assume that acute kidney injury is an iatrogenic condition, caused by poor medical care, when in fact it is indicative of the severity of the underlying medical condition. Finally, most patients will not be familiar with "acute kidney injury" and informing them of the presence of the condition may engender significant stress or anxiety without offering a tangible benefit.

Prior to pursuing a waiver of informed consent, however, we weighed the issues of patient autonomy with the feasibility of actually obtaining consent from each patient. In order to obtain consent, we would need to either rapidly enroll all patients with an AKI at the moment of their AKI occurrence or prospectively inform all patients about the possibility of developing an AKI so that they would have already been consented at the moment of their AKI occurrence. The former method would be inefficient and utilize significant time and effort by study personnel, as about 10% of all hospitalized patients experience AKI. The latter method would risk loss of confidentiality for a significant number of hospitalized patients, ~90% of which will never go on to develop AKI. In addition, informing patients about the presence of an AKI will act as a separate alert of sorts, as patients in the control arm may inadvertently relay this information to providers or be placed in the position of withholding information to providers (in both the control and experimental arms), which may undermine the physician-patient relationship.

We also felt that the harm to patients with a waiver of informed consent will be minimal, as informing providers of the presence of an AKI is a low-risk intervention relying on a novel presentation of data that is theoretically already available.

Data Dissemination

As we recognize the novel strategies and potential impact of our trial, we are committed to the open and timely dissemination of our data. Our trial has been registered with clinical trials.gov (NCT02753751) and will be continually reviewed and updated. We intend to submit the results

of our trial no later than one year following the completion date, and will include aggregate-level primary and secondary outcomes, participant demographics, statistical analyses and any adverse events. We also intend to disseminate information through publications and through the submission of our results the NIH data sharing repository.

Discussion

Acute kidney injury significantly increases the risk of morbidity and mortality in hospitalized patients. We designed a multi-center, randomized, controlled trial to determine whether the use of an AKI alert system will improve outcomes with regards to patients with this condition. The design of this trial was challenging for several reasons, presented above and summarized here. First, we needed to create a novel electronic alert system specific to this clinical trial; to do this, we needed to work within the limitations of the Epic electronic medical record system. Second, the choice of a composite outcome of progression to AKI, inpatient dialysis, and inpatient death within 14 days of randomization was carefully chosen. Our process outcomes were carefully chosen as well, with a balance between utility of the best practice outcome and feasibility of measurement. Finally, the ethical issues associated with a lack of informed consent were carefully considered.

Randomized trials are of utmost importance to prevent implementation of alert systems that not only lack any demonstrable benefits on clinician behavior or patient outcomes but may also precipitate unforeseen consequences or burdens on the healthcare system.[17] The potential utility of an alert system is complicated by a variety of patient- and provider-specific factors that must be considered before its implementation. Positive outcomes on clinical efficacy should be

weighed against potential risks. As an example, one frequently documented phenomenon, alert fatigue, is a decreased attention to alerts due to frequent or overabundant alerting.[18-20] This may not only lead to lack of efficacy in the studied alert, but it can negatively impact pre-existing alerts once deemed successful. Further, as alert override from physicians is a common problem of current alerting systems, careful thought must be put into design and implementation of the alert so as to create elements that are likely to increase provider adherence and thus improve alert success.[21-25] User feedback and positive user perception of the benefits of alerting are critical in creating successful alert systems that are well-received by providers.[26,27]

In conclusion, through a reiterative process of design, implementation, and testing, we have developed an autonomous AKI alert coupled to an automated trial screening, enrollment, and randomization engine. This approach decreases the costs of such a trial dramatically, while simultaneously increasing generalizability (as virtually all eligible patients are enrolled). While this approach is not feasible for all clinical trials, especially those utilizing novel therapeutics, it is an ideal system to rigorously study systems-based interventions.

Authors' Contributions

All authors contributed substantially to the conception, design, drafting, and revising of the work. Final approval of the current version was given by all authors and all agree to be accountable for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Ethics Approval

This work was approved by the Yale Institutional Review Board with a waiver of informed consent (IRB Protocol ID 1604017596).

Transparency Statement

The lead author (FPW) affirms that this manuscript represents an honest, accurate, transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned and registered have been explained.

Figure Legends:

Figure 1: The "pop-up" electronic alert. The alert gives relevant information regarding recent creatinine values and provides access to an AKI order set as well as relevant trial information.

Figure 2: Histogram demonstrating the number of alerts received by providers during the pilot phase.

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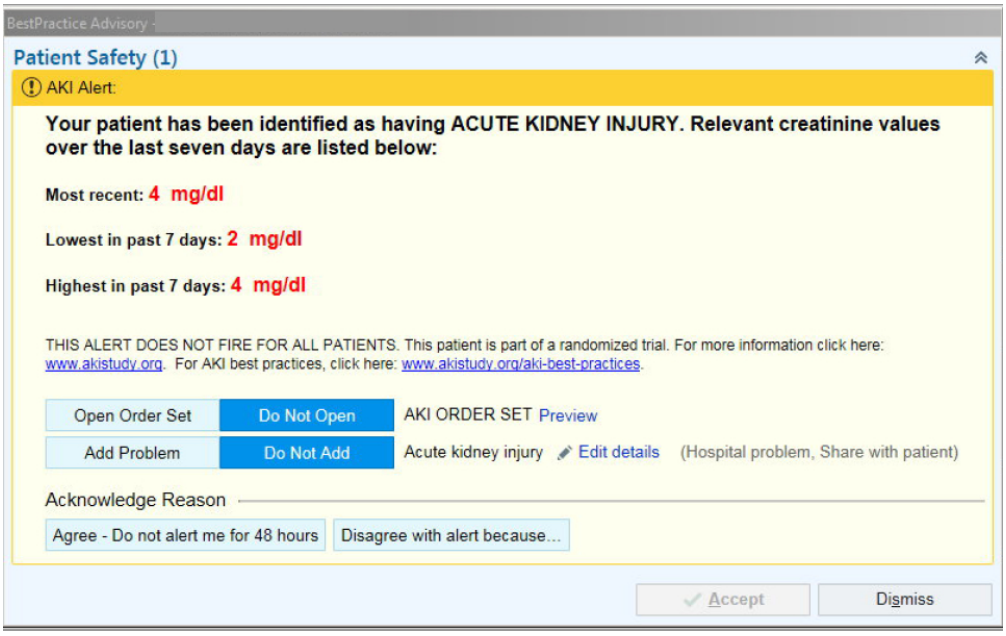
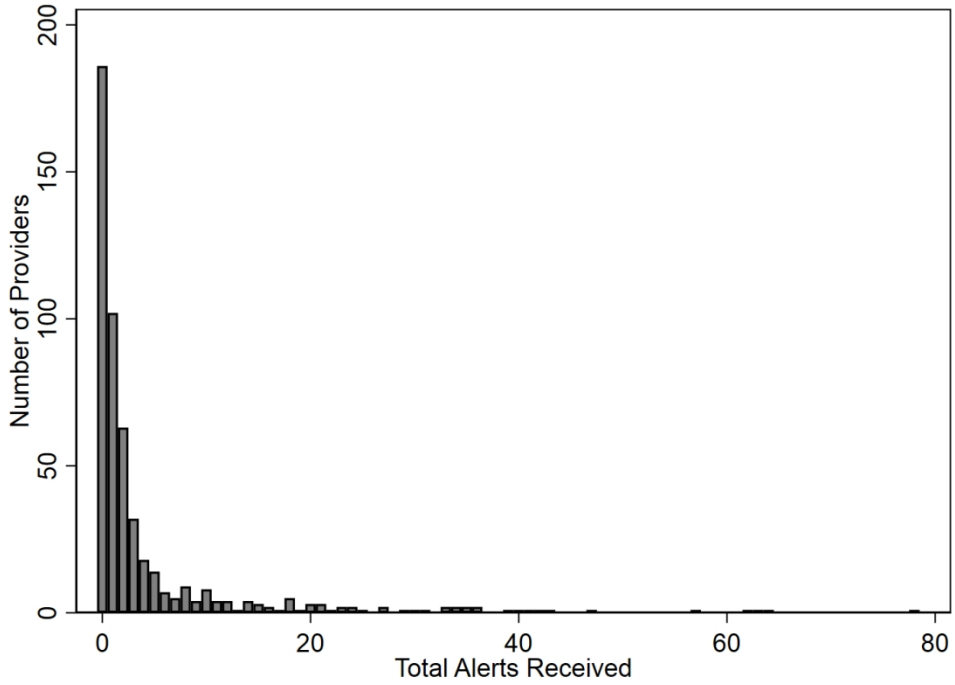


The "pop-up" electronic alert. The alert gives relevant information regarding recent creatinine values and provides access to an AKI order set as well as relevant trial information.



Histogram demonstrating the number of alerts received by providers during the pilot phase.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	Supplemental Material
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 24

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Supplemental Material
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A no comparators being used other than usual care
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	8

		applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A subjects are unaware of their participation in the trial and do not require adherence
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A done solely electronically via EMR
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Supplemental Material

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A Patients are blinded and cannot discontinue intervention
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplemental Material
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplemental Material
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported	Supplemental Material

		adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplemental Material
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Supplemental Material
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A This trial has a waiver of informed consent
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplemental Material
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplemental Material
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants,	23

		healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Supplemental Material
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Supplemental Material
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Electronic Alerts for Acute Kidney Injury Amelioration (ELAIA-1): A Completely Electronic, Multi-Center, Randomized Controlled Trial: Design and Rationale

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Electronic **A**lerts for Acute Kidney **I**njury **A**melioration **(ELAIA-1):** A Completely Electronic, Multi-Center, Randomized Controlled Trial: Design and Rationale

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Abstract:

Introduction: Acute kidney injury (AKI) is common among hospitalized patients and under-recognized by providers yet carries a significant risk of morbidity and mortality. Electronic alerts for AKI have become more common despite a lack of strong evidence of their benefits. We designed a multicenter, randomized, controlled trial to evaluate the effectiveness of AKI alerts. Our aim is to highlight several challenges faced in the design of this trial, which utilizes electronic screening, enrollment, randomization, intervention, and data collection.

Methods and analysis: The design and implementation of an electronic alert system for AKI was a reiterative process involving several challenges and limitations set by the confines of the electronic medical record system. The trial will electronically identify and randomize 6,030 adults with AKI at 6 hospitals over a 1.5 – 2 year period to usual care versus an electronic alert containing an AKI-specific order set. Our primary outcome will be a composite of AKI progression, inpatient dialysis and inpatient death within 14 days of randomization. During a one-month pilot in the medical intensive care unit of Yale New Haven Hospital**,** we have demonstrated feasibility of automating enrollment and data collection. Feedback from providers exposed to the alerts was used to continually improve alert clarity, user friendliness, and alert specificity through refined inclusion and exclusion criteria.

Ethics and dissemination: This study has been approved by the appropriate ethics committees for each of our study sites. Our study qualified for a waiver of informed consent as it presents no more than minimal risk and cannot be feasibly conducted in the absence of a waiver. We are committed to open dissemination of our data through clinicaltrials.gov and submission of results

to the NIH data sharing repository. Results of our trial will be submitted for publication in a peer-reviewed journal.

Trial Registration: clinicaltrials.gov NCT02753751

Keywords: Acute kidney injury, acute renal failure, electronic health record, randomized, alert, clinical decision support

Article Summary:

This manuscript discusses the design, ethical framework, and plan of execution of a multicenter randomized controlled trial of electronic acute kidney injury alerts.

Strengths and Limitations of this Study:

- A multicenter, randomized controlled trial which is the first of its kind to rigorously test the efficacy of an electronic alert at multiple hospitals before broad implementation.
- Carefully designed selection criteria to reduce the rate of false positives.
- Complete reliance on the electronic medical record for subject screening, enrollment, and randomization and delivery of the intervention, which reduces cost and increases scope of data collection, efficiency and generalizability.
- Reliance on the electronic medical record presents limitations in alert design and randomization methods.

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function, which results in the accumulation of metabolic waste products, as well as dysregulation of volume status, electrolyte and acid-base balance. This condition is common, estimated to occur in about 5-20% of all hospitalized patients, and carries a significant, independent risk of mortality of up to 20% in some studies.[1-3]

International guidelines for the treatment of AKI focus on appropriate management of drug dosing, avoiding nephrotoxic exposures, and careful attention to fluid and electrolyte balance.[2] Early nephrologist involvement may also improve outcomes in the care of acute kidney injury.[3] Without appropriate provider recognition of AKI, however, none of these measures can be taken, and patient outcomes may suffer. Unfortunately, AKI (which is asymptomatic) is frequently overlooked by clinicians and carries a substantial cost, morbidity, and mortality burden.[1] In a prior study at a tertiary care academic hospital, we found that only 43% of patients had documentation of AKI in the medical record and that AKI documentation was associated with decreased mortality, adjusted for admission type and severity of illness.[4] Further, patients with AKI often continue to be exposed to kidney-toxic medications.[5,6]

Automated alert systems have emerged as a strategy to influence clinician detection of specific clinical states and subsequent behavior. Several randomized trials have demonstrated the efficacy

of using alerts, particularly in minimizing drug interactions in hospital settings.[7-11] In 2014, our group was the first to conduct a pilot, randomized trial of electronic alerts for acute kidney injury.[12] The trial, which randomized 2373 patients with AKI, found that alerting a single physician to the presence of AKI did not improve the course of AKI or reduce dialysis or death rates. Our pilot study demonstrated that there is clinical equipoise regarding the effectiveness of alerting, and that alerting to the presence of this condition should not be considered standard of care.

However, our pilot study had several limitations which we address in a new randomized trial. The prior study was conducted in a single hospital, and the alert itself did not describe specific actions that a provider could take in response to the alert. The alert was delivered only once, to a single provider (and a unit pharmacist) without contextualization (i.e., it occurred outside of the relevant electronic health record). In the present trial, we expand upon our prior study to determine the efficacy of an electronic alert system to modify provider behavior and reduce patient outcomes. We hypothesize that an electronic AKI alert with an attached AKI-specific order set will improve best practices in regards to care of hospitalized patients with acute kidney injury and improve rates of progression of AKI, dialysis, or death in hospitalized patients. This trial is notable for its reliance on the EHR to screen, enroll, randomize, and deliver the intervention to patients. It further differs from our pilot study in that alerts are integrated at the point of care, that they are delivered to multiple providers, and in its use of a multicenter design which allows for assessment of heterogeneity of alert effect across different hospital types with diverse patient populations.

METHODS AND ANALYSIS

The study design was approved by the Yale Institutional Review Board (Yale IRB# 1604017596) and is registered under clinicaltrials.gov NCT02753751. It operates under a waiver of informed consent (see *ethics* section). The protocol conforms to the principles of the Declaration of Helsinki and the full study protocol is accessible at www.akistudy.org. This manuscript was submitted using the SPIRIT reporting guidelines.[13]

This is a multi-center, parallel-group, randomized, controlled trial to evaluate the efficacy of an AKI alert system for hospitalized patients with acute kidney injury. The six participating centers are described in Table 1 and were selected on the basis of their shared use of an electronic health record (Epic Systems, Verona WI). AKI alerts were not previously present at any of the sites, with the exception of Yale New Haven Hospital, where we piloted the alert for a month prior to beginning the trial (discussed below). This piloting phase was followed by a month-long washout period where no alerts were firing to reduce contamination of the study. The trial began on March 26th, 2018 and is expected to enroll patients for 1.5 to 2 years.

Table 1: Participating centers in the ELAIA-1 trial

INSTITUTION	LOCATION	TYPE	TEACHING	BEDS
Bridgeport Hospital	Bridgeport, CT	Community	Yes	383
Greenwich Hospital	Greenwich, CT	Community	Yes	206
The Hospital of St. Raphael	New Haven, CT	Community	Yes	511

Lawrence and Memorial Hospital	New London, CT	General/acute care	No	280
Yale New Haven Hospital	New Haven, CT	Acute/Tertiary	Yes	1,030
Westerly Hospital	Westerly, RI	Community	No	60

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, design of the study, or outcome assessment.

Participants

All inpatients 18 years of age or older at the six participating centers who develop AKI will be automatically enrolled into the trial. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define AKI as an increase in serum creatinine concentration of 0.3 mg/dL above baseline within 48 hours or a relative increase of 50% above baseline within 7 days .[2] Because of limitations within Epic's best practice alert framework, we define AKI in our study as a 0.3 mg/dL increase above the lowest proceeding creatinine value within a 48 hour period, or a 50% increase above the lowest proceeding creatinine value within a 7 day period. This slight variation on the KDIGO definition avoids the need for imputation of a baseline creatinine value and potentially artificially prolonged AKI duration. AKI may also be defined by urine output criteria, however, because it is difficult to collect the necessary output data in most (non-ICU) patients, this component was not used in our definition.

Exclusion criteria

Our exclusion criteria are designed to reduce the rate of "false-positive" alerting (alerts sent for individuals without true AKI). Patients with initiation of dialysis prior to AKI onset and with an end-stage kidney disease (ESKD) diagnosis code will be excluded. Patients with an initial serum creatinine ≥ 4.0mg/dL will also be excluded due to a lack of consensus definitions of AKI in this population. Patients admitted to hospice services or who are made "comfort measures only" will also be excluded, as the use of an electronic alert is not expected to impact their care. We will also exclude patients within 6-months of kidney transplant, as these individuals are monitored closely for changes in kidney function when hospitalized.

Intervention

Patients will be randomized to either usual care (UC) or to the AKI electronic alert system (Alert). The alert consists of a “pop-up” generated within the EMR when the provider accesses a patient record (Figure 1). [Insert Figure 1.]

The electronic alert text was designed to inform providers of the presence of acute kidney injury in their patient, as well as provide a minimum and maximum creatinine value within the prior 7 days. Therefore, the language was kept broad and simple. The alert reads “Your patient has been identified as having acute kidney injury. Relevant creatinine values over the last seven days are listed below.” The most recent creatinine value, as well as the lowest and highest values in the past 7 days, will be listed. This is followed by the following statement “THIS ALERT DOES

NOT FIRE FOR ALL PATIENTS. This patient is part of a randomized trial. For more information, click here: www.akistudy.org." The electronic alert also includes a link to an AKI order set, which includes labs and imaging to further work-up acute kidney injury. The order set was designed so as not to promote or increase the use of any one particular therapeutic strategy, as this could vary from patient to patient. While no patient-specific guidance or recommendations are made, our trial website does include a list of KDIGO clinical practice guidelines for AKI care, which can bereferenced by clicking the link in the alert. Finally, at the bottom of the alert, an option to either "agree" or "disagree" with the alert is provided. [Insert Figure 2.]

In our previous study, only one primary in-house provider received an alert per patient, however we hypothesized that creating a more comprehensive alerting system may improve alert efficacy. Providers who will receive an alert include physicians, physician assistants (PAs), nurse practitioners (NPs) and advanced practice registered nurses (APRNs). Any of the above type of providers, regardless of relationship to the patient, will receive the alert when the patient's chart is opened. This population of providers was chosen as (unlike nurses, pharmacists, or medical students) they are able to enter and discontinue diagnostic and treatment orders that may impact the course of AKI.

Mode and invasiveness of alerting were important considerations of the present study. In our previous study, we used a text-based paging system for alerting providers to the presence of acute kidney injury. This was a minimally invasive approach that was disconnected with provider activity in the EMR. In this trial, the alert occurs at the point of care, and is linked to

both an AKI order set containing generic options for further work-up as well as a link to our study website that containsevidence-based practice guidelines.

Alert frequency

The AKI alert will be displayed to the relevant provider whenever the patient's chart is opened while they have AKI. If the provider "dismisses" the alert, it will continue to "pop-up" on each subsequent opening of the patient's medical record by that provider. The alert will stop firing for the provider under the following conditions:

- The provider acknowledges the alert by "agreeing" that AKI is present, or by "disagreeing" that AKI is present with an accompanying explanation (alert will then be suppressed for 48 hours)
- The patient's most recent creatinine no longer meets criteria for AKI
- The patient receives an order for hemodialysis, continuous renal replacement therapy, or peritoneal dialysis
- The patient is transferred to the hospice service, is made comfort measures only, or dies
- The patient is discharged from the hospital

Though we recognize that repeated alerts may become onerous and lead to alert fatigue[14], we felt that physicians may not recognize the presence of acute kidney injury or fully read the alert if only provided with one alert. In addition, we wanted to study the utility and usefulness of the AKI order set and/or use of the link for KDIGO clinical practice guidelines, which would be more likely to occur if providers view and read the alert multiple times. In order to counteract

potential alert fatigue, we do give providers the option to suppress the alert, as stated above. Further, because our definition of AKI is based on changes in creatinine compared to a lowest previous creatinine value within either 48 hours or 7 days, alerting will stop if a patient's creatinine remains unchanged, or undergoes little change, for an extended period of time that would take the patient outside of this window. This can help reduce alert fatigue by stopping alerts on patients for which AKI is presumably already well-known.

We are also aware that repeated alerting may lead to variable "dosing" of the intervention. Because our prior study involved one alert per patient, a uniform intervention was guaranteed for all patients in the alert arm. Here, it is feasible for patients to experience different "doses" of the alert, dependent upon the duration of AKI, frequency and timing of EMR access, and provider response to the alerts. As such, this trial is best conceptualized as an attempt to measure the effectiveness of an alert protocol rather than of an individual alert *per se*.

Randomization

Simple randomization is achieved within the Epic EMR system using an internal random number rule. Randomization occurs the first time the patient's chart is opened by an eligible provider after an AKI-defining creatinine value has been reported into the EHR. If the patient has AKI according to KDIGO creatinine criteria, and if the patient meets all other inclusion and exclusion criteria, the patient is automatically enrolled and randomized. Once randomized into either arm, the patient remains in this arm for the duration of their hospital stay. Beyond the primary intervention, no further tests or procedures will be performed on subjects in this trial.

Though commonly used in clinical trials, a permuted block randomization method was not utilized as this EHR has neither the functionality to generate permuted block lists or to import external randomization lists. Allocation concealment is maintained as the alert process is completely automated and performed within the EHR. In addition, we chose not to randomize at the provider level because this was deemed infeasible; patients at the participating hospitals are cared for by multiple providers, who may change during the course of a patient's hospital stay. While cluster randomization is a commonly used strategy that could reduce the risk of contamination across study arms, this method was deemedinfeasible in this study given the limited number of clusterable entities (i.e. six hospitals). Ward-based clustering would not be feasible given the fact that physicians (especially consultants) see patients throughout a given hospital. Additionally, because our six study sites range from small community hospitals to larger tertiary care centers, it would be difficult to assess differences between study arms containing confounders arising from potentially vastly different patient and provider populations. Performing simple randomization at the patient level will allow for sub-analyses of alert efficacy independently at each hospital and in individual wards. Stepped-wedge clustering has also been increasingly used in the evaluation of interventions related to service delivery. This method allows for both inter- and intra-cluster comparisons. However, the effect across study arms is likely to be confounded by unanticipated temporal and seasonal trends. Further, it would be difficult for study investigators to remain blinded as the time of crossover would be known. Both study designs have inherently greater statistical complexity to account for intracluster correlation and reduced statistical efficiency that does not outweigh their advantages. Given these considerations, we believe that a simple randomization scheme would be best for our study

design, however, we do recognize that this does have important implications with regards to contamination (see below).

Blinding

Participants and the study team will be blinded to the intervention, though obviously care providers will be aware of treatment assignment.

Clinician Outreach

While the unit of randomization is the patient, clinicians may also be considered subjects of this research. We will engage in pre-trial and periodic outreach to all clinicians who may be exposed to this study, informing them of the nature of the study, the fact that it is a randomized trial, and that alerts do not fire for all patients with AKI. We will additionally inform them that limited data is being collected regarding provider behavior. The pre-trial education will occur in the form of short education presentations at group and departmental meetings given by either the study's principle investigator (a clinical nephrologist) or a study coordinator. The study coordinator will also be at each site when the alerts become active in order to provide further provider education and answer any questions. Periodic site visits by the study coordinator or check-ins with local site investigators will occur on a monthly basis at each site to ensure that the alerts are functioning correctly and to reeducate any new providers on the floors. While we believe clinician education is important, we feel it's best that this process remain relatively simple to allow for broader adoption in the future should alerting prove beneficial. Further, the

alert pop-up contains methods to contact the study team. Most notable, if "disagree" is clicked, a free-text box is opened that allows providers to communicate their concern directly to the team. While piloting the popup in pre-trial activities, we used these responses to further tailor the language of the alert. We will also make it clear that data subject to clinician behavior (such as AKI documentation) will NOT be linked to individual clinicians.

Primary Outcome

The primary outcome will be a composite of progression to a higher stage of AKI, inpatient dialysis and inpatient death within 14 days of randomization, chosen such that we can objectively measure hard clinical outcomes of AKI that can be easily extracted from the EHR. Severity of AKI is strongly associated to longer-term outcomes, such as Chronic Kidney Disease (CKD) and End-Stage Kidney Disease (ESKD), while dialysis and death allow us to capture events that limit the rise in creatinine and that, if not accounted for, would potentially lead to missed cases of severe AKI. We chose this time frame for outcome assessment as the effect of an AKI alert might be diluted over time as more issues arise during the hospitalization. However, we also recognize that this time frame will potentially capture outcomes that occur in a period of time representing Acute Kidney Disease (AKD), a period of continued kidney dysfunction after AKI.[15]

Secondary outcomes of interest

Secondary outcomes of interest are listed in Table 2. Many of these are process measures, as we are particularly interested in measures that may change as a result of AKI alerts. In determining secondary outcomes of interest, we needed to balance outcomes that would be of interest to clinicians and other care providers with the feasibility of accurately determining those specific outcomes. This was particularly relevant for "best practices" such as dose-adjustment for medications, which can be somewhat subjective and thus requires direct chart review for determination.

To operationalize our "duration of AKI" endpoint, we define "C1" as the AKI-defining creatinine, and "C0" as the lowest preceding creatinine in the past 48 hours or past seven days depending on which KDIGO AKI criteria was met. For those defined by both, C0 will be the lower of the two creatinine values. Cessation of AKI will occur when a subsequent creatinine measure is within 0.3 mg/dl or 50% of C0, again depending on the KDIGO AKI criteria initially met (and within both if both criteria were met). While C0 may not represent true "normal" kidney function for a patient, selecting this time point avoids imputation of a baseline while avoiding potentially artificially prolonged AKI duration. Further, as it is conceivable that patients can be discharged prior to recovery and receive no follow-up creatinine measurements, we will evaluate differences in duration of AKI through the use of Kaplan-Meier estimators, allowing for censoring at death or discharge.

Table 2: Secondary outcomes of interest

ENDPOINT AND DEFINITIONS	DATA SOURCE
Mortality outcomes	

Inpatient mortality	Hospital record
Dialysis outcomes	
Inpatient dialysis	Order entry system
Discharged on dialysis	Social work records
Renal Failure Outcomes	
Percent who progress to Stage 2 AKI	Laboratory values
Percent who progress to Stage 3 AKI	Laboratory values
Duration of AKI	Laboratory values
Readmission Rate and Costs	
30-day readmission rate	Hospital record
Cost of index hospitalization	Billing records
Individual "Best Practice" Outcomes (proportion achieved per patient in study arm during index hospitalization)	
Contrast administration	Order entry system
Fluid administration	Order entry system
Aminoglycoside administration	Order entry system
NSAID administration/cessation	Order entry system
ACE inhibitor administration/cessation	Order entry system
Urinalysis order	Order entry system
Documentation of AKI	Post-discharge ICD-10 codes
Monitoring of creatinine	Order entry system
Monitoring of urine output	Hospital Record

Renal consult	Direct chart review
Provider awareness outcomes	
Chart documentation of AKI (by post-discharge ICD-10 codes)	Billing records
Chart documentation of AKI (adjudicated)	Direct chart review

AKI: acute kidney injury; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin converting enzyme

Subgroup analysis

The effect of the alert may differ based on several patient characteristics. We have therefore pre-specified several sub-groups of interest that are outlined in Table 3 and that will be considered hypothesis-generating for the future design of targeted alerts towards populations that are more likely to benefit from an alert system. Additionally, because we are enrolling patients across six hospitals that vary in size, type, and patient population, we will perform an exploratory analysis to determine the efficacy of alerts independently at each site.

Table 3: Planned subgroup analyses and justification

Subgroup of primary interest	**Justification**
Surgical patients (defined by admission to a surgical team)	Risk of under-documentation (reference)

Subjects with baseline creatinine <1.0mg/dl	AKI occurs when creatinine in "normal range"
Subjects with baseline creatinine <0.5mg/dl	AKI occurs when creatinine in "normal range"
Females	Lower rate of creatinine increase after AKI (reference)
African Americans	Higher rate of creatinine increase after AKI (reference)
Elderly (age >65, age >70 and age >75)	Lower rate of creatinine increase after AKI (reference)
Subjects in an ICU at the time of the alert	AKI may be overlooked in the setting of multiple clinical problems
Subjects who enter the study based on a 50% increase in creatinine vs. a 0.3mg/dl increase in creatinine vs both	Clinicians may be less likely to recognize a 0.3mg/dL change vs a 50% change

Contamination

As providers are not randomized and will be aware of patients who are randomized to the experimental arm, there is a risk of contamination of the intervention. Providers may use the information provided in the AKI alert (i.e. definition of AKI, best practices with respect to AKI care, etc.) to improve their ability to detect AKI in patients not randomized to the experimental

arm. In addition, improved knowledge with respect to the definition of an acute kidney injury and its appropriate management may improve the ability to detect AKI over time. In order to address this issue, we will examine the outcome rate in the control arm over time; if the outcome rate in the control arm improves over time, this may suggest contamination.

Beyond that, we will establish a pre-trial baseline cohort of patients that would be enrolled were the trial actively recruiting by retrospectively collecting a year's worth of pre-trial patient data from each study site. While temporal shifts in treatment may change outcomes over time independent of alerting, a significant improvement in AKI outcomes in the control arm of the trial vs. the pre-trial cohort would further suggest contamination.

Finally, it is possible that providers exposed to alerts may actually be at risk of increased *inattention* to AKI in patients of the control arm, as they may become accustomed or dependent upon receiving an alert as recognition of AKI. We will attempt to mitigate this through periodic outreach to clinicians and explicitly stating on the alert that not all patients with AKI trigger an alert.

Statistical Analysis

The primary outcome will be analyzed as a simple combination of progression of AKI, dialysis, and death at 14 days after randomization or at discharge (whichever comes first). If any one of these three elements is positive, the composite outcome will be considered positive. The primary analysis will utilize the intention to treat principle. The proportion of patients who experience

the primary outcome in the intervention and control groups will be compared by the chi-square test with Mantel-Haenszel correction for the 6 study strata (by hospital). Statistical significance will be based on a two-sided p-value of <0.05. As all pre-specified secondary outcomes are categorical in nature, these will be similarly analyzed, using the chi-square test with Mantel-Haenszel correction. We will not be correcting for multiple testing, especially because many of our secondary outcomes are likely correlated, making a true Bonferoni correction overly conservative. Therefore, we consider these outcomes as hypothesis-generating only, and any significant findings should be further explored.

Power and sample size considerations

To estimate the sample size, we conducted a retrospective analysis of patients with AKI at 3 of the 6 study hospitals. The composite outcome of progression of AKI, dialysis, or death occurred in 24.5% of 29,027 individuals with AKI in this analysis. A 20% reduction in this proportion (to 19.6%) would be clinically meaningful. To that end, a sample size of 2512 in each arm achieves 90% power to detect a difference this large at a two-sided alpha of 0.05. This was calculated with the PASS software package version 13.0[16], using the continuity-corrected form of the Cochran-Mantel-Haenszel test to account for the 6 hospital strata.[17,18] This gives a total population of 5,025 individuals with AKI. We have elected to increase this number by 20% to account for potential contamination of the effect across study arms, leading to a final sample size of 6,030 individuals.[19] In addition to adequately powering for the primary clinical outcome, this sample size will allow us to detect at least a 16% increase in the odds of more best practices being completed in the intervention group.

Interim Analysis

We plan to have one interim analysis at the mid-point of the trial when 50% of patients have been enrolled. The interim analysis will allow us to alter the sample size or stop the trial earlier for ethical considerations, unexpected adverse events or high efficacy. The trial will stop for declaring efficacy if the effect size is large. We will use the O'Brien and Fleming stopping rule to stop the trial at a p-value of 0.001 for efficacy.[20] Alerting harm will be also be assessed using the primary outcome, but the threshold for stopping the study will be greater, at a p-value of 0.005. The DSMB will be unblinded to the study outcomes for these assessments, but the study team will remain blinded throughout.

Pre-intervention data

Pilot in the Medical Intensive Care Unit (MICU)

Prior to the implementation of the electronic alert across all six hospital systems, we piloted the alert from 01/08/2018 to 02/08/2018 in the medical intensive care unit at Yale-Haven Hospital. The purpose of this pilot phase was to evaluate the appropriateness of alerting, to solicit feedback from providers, and to ensure that the electronic methods of data capture were valid. There were 77 patients randomized (37 to alert, and 40 to control). The alert fired a total of 2,355 times, a median (IQR) of 48 (23- 89) alerts per patient. Of 509 providers eligible to receive alerts, 323 providers received at least one, with a median of 1 (0 – 9) alerts per eligible provider (Figure 2).

The median number of providers per patient was 17 (9-24), which may explain the low number of alerts seen per provider despite a high total number of alerts fired. The maximum number of alerts received by a single provider over the 30 days of the pilot was 78 alerts from 12 different patients. That provider was an acute care nurse practitioner assigned to the MICU for the duration of the pilot. Median alert duration was 0.84 (0.47-1.64 days. [Insert Figure 3.]

Outcomes for all randomized patients were as expected for a medical intensive care unit population. Inpatient death occurred in 29 (37%) of patients, while 4 (5.1%) were discharged home. The remainder of patients were discharged to a nursing facility, hospice, or transferred to another medical facility. In terms of AKI outcomes, the majority of these patients (52%) never had progression of AKI, 29% progressed to stage 2, and 18% progressed to stage 3.

Several iterations to the alert were made over the course of the pilot in response to provider feedback and internal testing. These are summarized in Box 1:

Change	Motivation
Excluded patients with “deceased” status	Occasional alerting on patients who had recently died was ghoulish and unactionable
Modified language to make it clear that “agreeing” with alert suppresses future alerts for themselves only	Providers are eager to find ways to suppress alerts once they have been alerted
Extended the “prior dialysis” exclusion criterion to one year	Some chronic dialysis patients would initially lead to an alert

Excluded providers who cannot enter orders	AKI Order set is not useful for individuals (such as nurses, medical students) who are unauthorized to enter orders.

Box 1: Summary of changes made to alerting during the piloting of the alert system.

ETHICS AND DISSEMINATION

Ethical Issues

This study posed several ethical issues that are worthy of discussion. First, in order to efficiently proceed with the study, we obtained a waiver of informed consent. United States federal guidelines require that in order to obtain a waiver of consent, 1) the research pose no more than minimal risk to the subject, 2) the waiver not adversely affect the rights and welfare of the subject, 3) the research could not be practicably carried out without a waiver and 4) whenever appropriate, the subjects be provided with additional pertinent information after participation. We felt that our study met all of the criteria noted above to qualify for a waiver of informed consent.

Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. We do not feel that post-facto informing of patients randomized in this trial is appropriate for several reasons. First, there is no guideline-based specific follow-up or intervention for acute kidney injury. Second, many patients may incorrectly assume that acute kidney injury is an iatrogenic condition, caused by poor medical care, when this is not always the case and, rather, their AKI is indicative of the

severity of the underlying medical condition. Finally, most patients will not be familiar with "acute kidney injury" and informing them of the presence of the condition may engender significant stress or anxiety without offering a tangible benefit. Because the intervention (alert) is a tool to make a provider aware of information already obtainable from the EHR, it is at the discretion of the provider to inform the patient of any relevant information regarding their AKI diagnosis, severity, and prognosis. We believe that the determination of the clinical impact and significance of AKI for a given patient rests with the primary providers and trust that they will act ethically with regards to the disclosure of the relevant medical information.

Prior to pursuing a waiver of informed consent, however, we weighed the issues of patient autonomy with the feasibility of actually obtaining consent from each patient. In order to obtain consent, we would need to either rapidly enroll all patients with an AKI at the moment of their AKI occurrence or prospectively inform all patients about the possibility of developing an AKI so that they would have already been consented at the moment of their AKI occurrence. The former method would be inefficient and utilize significant time and effort by study personnel, as about 10% of all hospitalized patients experience AKI. The latter method would risk loss of confidentiality for a significant number of hospitalized patients, ~90% of which will never go on to develop AKI. In addition, informing patients about the presence of an AKI will act as a separate alert of sorts, as patients in the control arm may inadvertently relay this information to providers or be placed in the position of withholding information to providers (in both the control and experimental arms), which may undermine the physician-patient relationship.

We also felt that the harm to patients with a waiver of informed consent will be minimal, as informing providers of the presence of an AKI is a low-risk intervention relying on a novel presentation of data that is theoretically already available.

Data Dissemination

As we recognize the novel strategies and potential impact of our trial, we are committed to the open and timely dissemination of our data. Our trial has been registered with clinical trials.gov (NCT02753751) and will be continually reviewed and updated. We intend to submit the results of our trial no later than one year following the completion date, and will include aggregate-level primary and secondary outcomes, participant demographics, statistical analyses and any adverse events. We also intend to disseminate information through publications and through the submission of our results the NIH data sharing repository.

Discussion

Acute kidney injury significantly increases the risk of morbidity and mortality in hospitalized patients. We designed a multi-center, randomized, controlled trial to determine whether the use of an AKI alert system will improve outcomes with regards to patients with this condition. The design of this trial was challenging for several reasons, presented above and summarized here. First, we needed to create a novel electronic alert system specific to this clinical trial; to do this, we needed to work within the limitations of the Epic electronic medical record system. Second, the choice of a composite outcome of progression to AKI, inpatient dialysis, and inpatient death

within 14 days of randomization was carefully chosen. Our process outcomes were carefully chosen as well, with a balance between utility of the best practice outcome and feasibility of measurement. Finally, the ethical issues associated with a lack of informed consent were carefully considered.

Randomized trials are of utmost importance to prevent implementation of alert systems that not only lack any demonstrable benefits on clinician behavior or patient outcomes but may also precipitate unforeseen consequences or burdens on the healthcare system.[21] The potential utility of an alert system is complicated by a variety of patient- and provider-specific factors that must be considered before its implementation. Positive outcomes on clinical efficacy should be weighed against potential risks. As an example, one frequently documented phenomenon, alert fatigue, is a decreased attention to alerts due to frequent or overabundant alerting.[22-24] This may not only lead to lack of efficacy in the studied alert, but it can negatively impact pre-existing alerts once deemed successful. Further, as alert override from physicians is a common problem of current alerting systems, careful thought must be put into design and implementation of the alert so as to create elements that are likely to increase provider adherence and thus improve alert success.[25-29] User feedback and positive user perception of the benefits of alerting are critical in creating successful alert systems that are well-received by providers.[30,31]

In conclusion, through a reiterative process of design, implementation, and testing, we have developed an autonomous AKI alert coupled to an automated trial screening, enrollment, and randomization engine. This approach decreases the costs of such a trial dramatically, while simultaneously increasing generalizability (as virtually all eligible patients are enrolled). While

this approach is not feasible for all clinical trials, especially those utilizing novel therapeutics, it is an ideal system to rigorously study systems-based interventions.

Authors' Contributions

Substantial contributions to the conception or design of the study: HIF, AG, NG, SL, HL, PMP, CRP, FPW

Acquisition, analysis, or interpretation of data: MM, YY, AB, BE, HIF, AG, SL, HL, PMP, CRP, EM, FPW

Drafting or revising the work critically: MM, MM, YY, AB, BE, HIF, AG, NG, SL, HL, PMP, CRP, EM, UU, FPW

Final approval of the draft to be published: MM, MM, YY, AB, BE, HIF, AG, NG, SL, HL, PMP, CRP, EM, UU, FPW

Agreement to be accountable for all aspects of the work and ensuring that questions related to accuracy or integrity are appropriately investigated and resolved: MM, MM, YY, AB, BE, HIF, AG, NG, SL, HL, PMP, CRP, EM, UU, FPW

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Ethics Approval

This work was approved by the Yale Institutional Review Board with a waiver of informed consent (IRB Protocol ID 1604017596) for Yale New Haven Hospital York Street Campus, Yale New Haven Hospital St. Raphael's Campus. Approval for the remainder of the sites was given by the Bridgeport Hospital Institutional Review Board with a waiver of informed consent. Bridgeport Hospital is listed under IRB #041801. Lawrence and Memorial Hospital is listed under IRB #051802. Westerly Hospital is listed under IRB #071808.

Transparency Statement

The lead author (FPW) affirms that this manuscript represents an honest, accurate, transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned and registered have been explained.

Figure Legends:

Figure 1: The "pop-up" electronic alert. The alert gives relevant information regarding recent creatinine values and provides access to an AKI order set as well as relevant trial information.

Figure 2: AKI order set. This order set can be opened directly from the electronic alert and contains generic options for further work-up.

Figure 3: Histogram demonstrating the number of alerts received by providers during the pilot phase.

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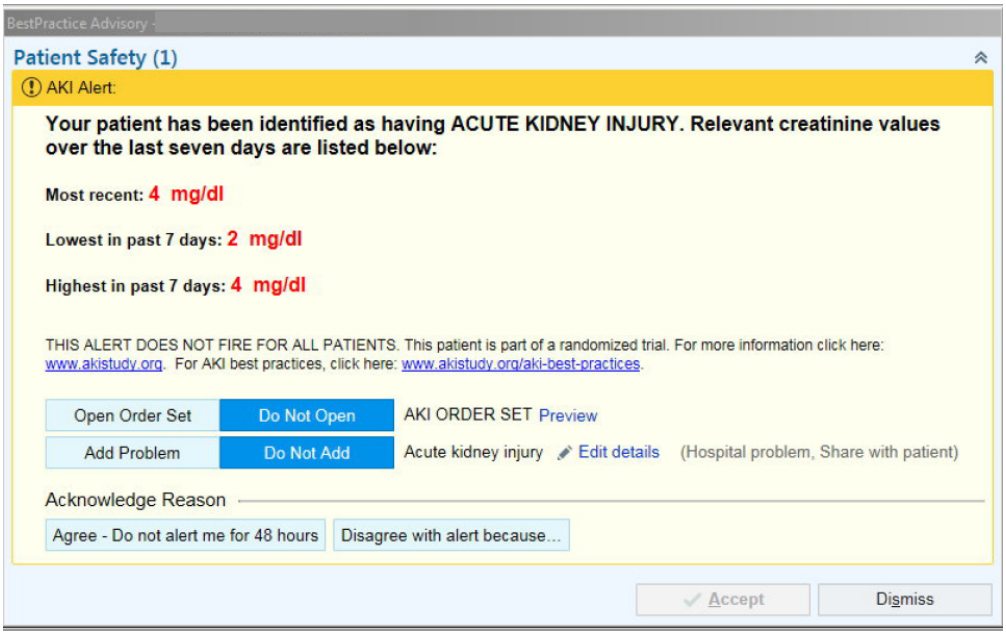


The "pop-up" electronic alert. The alert gives relevant information regarding recent creatinine values and provides access to an AKI order set as well as relevant trial information.

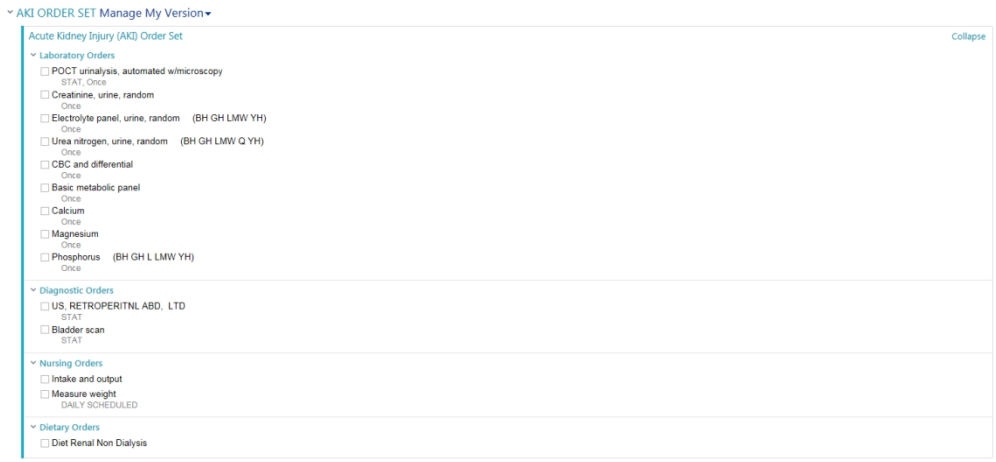
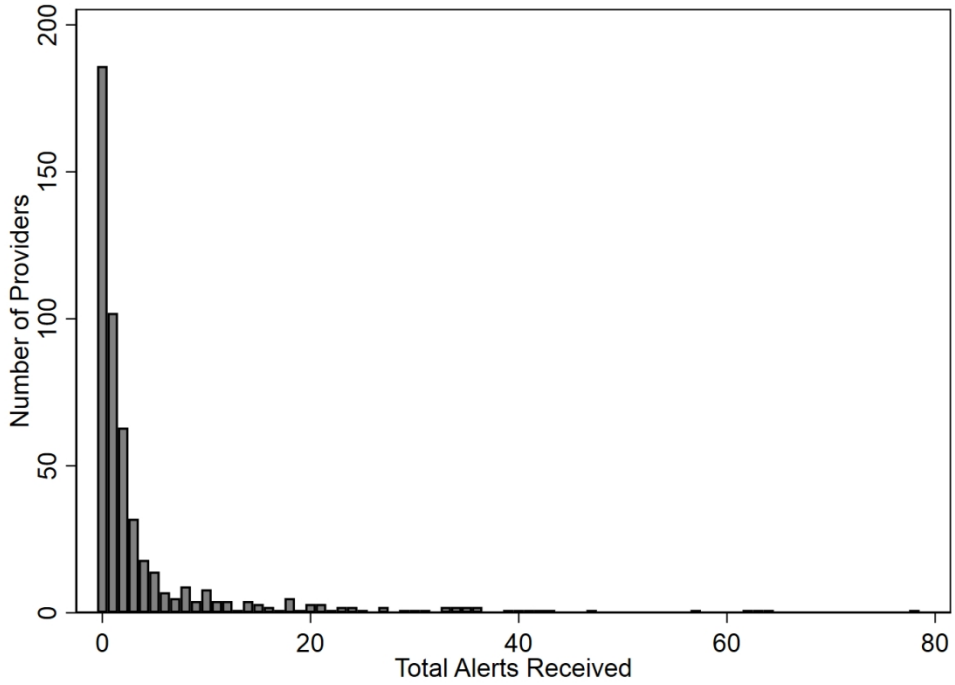


Figure 2: AKI order set. This order set can be opened directly from the electronic alert and contains generic options for further work-up.



Histogram demonstrating the number of alerts received by providers during the pilot phase.

Reporting checklist for protocol of a clinical trial.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	Supplemental Material
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 24

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Supplemental Material
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A no comparators being used other than usual care
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	8

		applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A subjects are unaware of their participation in the trial and do not require adherence
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A done solely electronically via EMR
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Supplemental Material

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A Patients are blinded and cannot discontinue intervention
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplemental Material
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplemental Material
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported	Supplemental Material

		adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplemental Material
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Supplemental Material
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A This trial has a waiver of informed consent
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplemental Material
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplemental Material
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants,	23

		healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Supplemental Material
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Supplemental Material
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Electronic Alerts for Acute Kidney Injury Amelioration (ELAIA-1): A Completely Electronic, Multi-Center, Randomized Controlled Trial: Design and Rationale

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Electronic **A**lerts for Acute Kidney **I**njury **A**melioration **(ELAIA-1):** A Completely Electronic, Multi-Center, Randomized Controlled Trial: Design and Rationale

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Abstract:

Introduction: Acute kidney injury (AKI) is common among hospitalized patients and under-recognized by providers yet carries a significant risk of morbidity and mortality. Electronic alerts for AKI have become more common despite a lack of strong evidence of their benefits. We designed a multicenter, randomized, controlled trial to evaluate the effectiveness of AKI alerts. Our aim is to highlight several challenges faced in the design of this trial, which utilizes electronic screening, enrollment, randomization, intervention, and data collection.

Methods and analysis: The design and implementation of an electronic alert system for AKI was a reiterative process involving several challenges and limitations set by the confines of the electronic medical record system. The trial will electronically identify and randomize 6,030 adults with AKI at 6 hospitals over a 1.5 – 2 year period to usual care versus an electronic alert containing an AKI-specific order set. Our primary outcome will be a composite of AKI progression, inpatient dialysis and inpatient death within 14 days of randomization. During a one-month pilot in the medical intensive care unit of Yale New Haven Hospital**,** we have demonstrated feasibility of automating enrollment and data collection. Feedback from providers exposed to the alerts was used to continually improve alert clarity, user friendliness, and alert specificity through refined inclusion and exclusion criteria.

Ethics and dissemination: This study has been approved by the appropriate ethics committees for each of our study sites. Our study qualified for a waiver of informed consent as it presents no more than minimal risk and cannot be feasibly conducted in the absence of a waiver. We are committed to open dissemination of our data through clinicaltrials.gov and submission of results

to the NIH data sharing repository. Results of our trial will be submitted for publication in a peer-reviewed journal.

Trial Registration: clinicaltrials.gov NCT02753751

Keywords: Acute kidney injury, acute renal failure, electronic health record, randomized, alert, clinical decision support

Article Summary:

This manuscript discusses the design, ethical framework, and plan of execution of a multicenter randomized controlled trial of electronic acute kidney injury alerts.

Strengths and Limitations of this Study:

- A multicenter, randomized controlled trial which is the first of its kind to rigorously test the efficacy of an electronic alert at multiple hospitals before broad implementation.
- Carefully designed selection criteria to reduce the rate of false positives.
- Complete reliance on the electronic medical record for subject screening, enrollment, and randomization and delivery of the intervention, which reduces cost and increases scope of data collection, efficiency and generalizability.
- Reliance on the electronic medical record presents limitations in alert design and randomization methods.

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function, which results in the accumulation of metabolic waste products, as well as dysregulation of volume status, electrolyte and acid-base balance. This condition is common, estimated to occur in about 5-20% of all hospitalized patients, and carries a significant, independent risk of mortality of up to 20% in some studies.[1-3]

International guidelines for the treatment of AKI focus on appropriate management of drug dosing, avoiding nephrotoxic exposures, and careful attention to fluid and electrolyte balance.[2] Early nephrologist involvement may also improve outcomes in the care of acute kidney injury.[3] Without appropriate provider recognition of AKI, however, none of these measures can be taken, and patient outcomes may suffer. Unfortunately, AKI (which is asymptomatic) is frequently overlooked by clinicians and carries a substantial cost, morbidity, and mortality burden.[1] In a prior study at a tertiary care academic hospital, we found that only 43% of patients had documentation of AKI in the medical record and that AKI documentation was associated with decreased mortality, adjusted for admission type and severity of illness.[4] Further, patients with AKI often continue to be exposed to kidney-toxic medications.[5,6]

Automated alert systems have emerged as a strategy to influence clinician detection of specific clinical states and subsequent behavior. Several randomized trials have demonstrated the efficacy

of using alerts, particularly in minimizing drug interactions in hospital settings.[7-11] In 2014, our group was the first to conduct a pilot, randomized trial of electronic alerts for acute kidney injury.[12] The trial, which randomized 2373 patients with AKI, found that alerting a single physician to the presence of AKI did not improve the course of AKI or reduce dialysis or death rates. Our pilot study demonstrated that there is clinical equipoise regarding the effectiveness of alerting, and that alerting to the presence of this condition should not be considered standard of care.

However, our pilot study had several limitations which we address in a new randomized trial. The prior study was conducted in a single hospital, and the alert itself did not describe specific actions that a provider could take in response to the alert. The alert was delivered only once, to a single provider (and a unit pharmacist) without contextualization (i.e., it occurred outside of the relevant electronic health record). In the present trial, we expand upon our prior study to determine the efficacy of an electronic alert system to modify provider behavior and reduce patient outcomes. We hypothesize that an electronic AKI alert with an attached AKI-specific order set will improve best practices in regards to care of hospitalized patients with acute kidney injury and improve rates of progression of AKI, dialysis, or death in hospitalized patients. This trial is notable for its reliance on the EHR to screen, enroll, randomize, and deliver the intervention to patients. It further differs from our pilot study in that alerts are integrated at the point of care, that they are delivered to multiple providers, and in its use of a multicenter design which allows for assessment of heterogeneity of alert effect across different hospital types with diverse patient populations.

METHODS AND ANALYSIS

The study design was approved by the Yale Institutional Review Board (Yale IRB# 1604017596) and is registered under clinicaltrials.gov NCT02753751. It operates under a waiver of informed consent (see *ethics* section). The protocol conforms to the principles of the Declaration of Helsinki and the full study protocol is accessible at www.akistudy.org. This manuscript was submitted using the SPIRIT reporting guidelines.[13]

This is a multi-center, parallel-group, randomized, controlled trial to evaluate the efficacy of an AKI alert system for hospitalized patients with acute kidney injury. The six participating centers are described in Table 1 and were selected on the basis of their shared use of an electronic health record (Epic Systems, Verona WI). AKI alerts were not previously present at any of the sites, with the exception of Yale New Haven Hospital, where we piloted the alert for a month prior to beginning the trial (discussed below). This piloting phase was followed by a month-long washout period where no alerts were firing to reduce contamination of the study. The trial began on March 26th, 2018 and is expected to enroll patients for 1.5 to 2 years.

Table 1: Participating centers in the ELAIA-1 trial

INSTITUTION	LOCATION	TYPE	TEACHING	BEDS
Bridgeport Hospital	Bridgeport, CT	Community	Yes	383
Greenwich Hospital	Greenwich, CT	Community	Yes	206
The Hospital of St. Raphael	New Haven, CT	Community	Yes	511

Lawrence and Memorial Hospital	New London, CT	General/acute care	No	280
Yale New Haven Hospital	New Haven, CT	Acute/Tertiary	Yes	1,030
Westerly Hospital	Westerly, RI	Community	No	60

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, design of the study, or outcome assessment.

Participants

All inpatients 18 years of age or older at the six participating centers who develop AKI will be automatically enrolled into the trial. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define AKI as an increase in serum creatinine concentration of 0.3 mg/dL above baseline within 48 hours or a relative increase of 50% above baseline within 7 days .[2] Because of limitations within Epic's best practice alert framework, we define AKI in our study as a 0.3 mg/dL increase above the lowest proceeding creatinine value within a 48 hour period, or a 50% increase above the lowest proceeding creatinine value within a 7 day period. This slight variation on the KDIGO definition avoids the need for imputation of a baseline creatinine value and potentially artificially prolonged AKI duration. AKI may also be defined by urine output criteria, however, because it is difficult to collect the necessary output data in most (non-ICU) patients, this component was not used in our definition.

Exclusion criteria

Our exclusion criteria are designed to reduce the rate of "false-positive" alerting (alerts sent for individuals without true AKI). Patients with initiation of dialysis prior to AKI onset and with an end-stage kidney disease (ESKD) diagnosis code will be excluded. Patients with an initial serum creatinine ≥ 4.0mg/dL will also be excluded due to a lack of consensus definitions of AKI in this population. Patients admitted to hospice services or who are made "comfort measures only" will also be excluded, as the use of an electronic alert is not expected to impact their care. We will also exclude patients within 6-months of kidney transplant, as these individuals are monitored closely for changes in kidney function when hospitalized.

Intervention

Patients will be randomized to either usual care (UC) or to the AKI electronic alert system (Alert). The alert consists of a “pop-up” generated within the EMR when the provider accesses a patient record (Figure 1). [Insert Figure 1.]

The electronic alert text was designed to inform providers of the presence of acute kidney injury in their patient, as well as provide a minimum and maximum creatinine value within the prior 7 days. Therefore, the language was kept broad and simple. The alert reads “Your patient has been identified as having acute kidney injury. Relevant creatinine values over the last seven days are listed below.” The most recent creatinine value, as well as the lowest and highest values in the past 7 days, will be listed. This is followed by the following statement “THIS ALERT DOES

NOT FIRE FOR ALL PATIENTS. This patient is part of a randomized trial. For more information, click here: www.akistudy.org." The electronic alert also includes a link to an AKI order set, which includes labs and imaging to further work-up acute kidney injury. The order set was designed so as not to promote or increase the use of any one particular therapeutic strategy, as this could vary from patient to patient. While no patient-specific guidance or recommendations are made, our trial website does include a list of KDIGO clinical practice guidelines for AKI care, which can bereferenced by clicking the link in the alert. Finally, at the bottom of the alert, an option to either "agree" or "disagree" with the alert is provided. [Insert Figure 2.]

In our previous study, only one primary in-house provider received an alert per patient, however we hypothesized that creating a more comprehensive alerting system may improve alert efficacy. Providers who will receive an alert include physicians, physician assistants (PAs), nurse practitioners (NPs) and advanced practice registered nurses (APRNs). Any of the above type of providers, regardless of relationship to the patient, will receive the alert when the patient's chart is opened. This population of providers was chosen as (unlike nurses, pharmacists, or medical students) they are able to enter and discontinue diagnostic and treatment orders that may impact the course of AKI.

Mode and invasiveness of alerting were important considerations of the present study. In our previous study, we used a text-based paging system for alerting providers to the presence of acute kidney injury. This was a minimally invasive approach that was disconnected with provider activity in the EMR. In this trial, the alert occurs at the point of care, and is linked to

both an AKI order set containing generic options for further work-up as well as a link to our study website that containsevidence-based practice guidelines.

Alert frequency

The AKI alert will be displayed to the relevant provider whenever the patient's chart is opened while they have AKI. If the provider "dismisses" the alert, it will continue to "pop-up" on each subsequent opening of the patient's medical record by that provider. The alert will stop firing for the provider under the following conditions:

- The provider acknowledges the alert by "agreeing" that AKI is present, or by "disagreeing" that AKI is present with an accompanying explanation (alert will then be suppressed for 48 hours)
- The patient's most recent creatinine no longer meets criteria for AKI
- The patient receives an order for hemodialysis, continuous renal replacement therapy, or peritoneal dialysis
- The patient is transferred to the hospice service, is made comfort measures only, or dies
- The patient is discharged from the hospital

Though we recognize that repeated alerts may become onerous and lead to alert fatigue[14], we felt that physicians may not recognize the presence of acute kidney injury or fully read the alert if only provided with one alert. In addition, we wanted to study the utility and usefulness of the AKI order set and/or use of the link for KDIGO clinical practice guidelines, which would be more likely to occur if providers view and read the alert multiple times. In order to counteract

potential alert fatigue, we do give providers the option to suppress the alert, as stated above. Further, because our definition of AKI is based on changes in creatinine compared to a lowest previous creatinine value within either 48 hours or 7 days, alerting will stop if a patient's creatinine remains unchanged, or undergoes little change, for an extended period of time that would take the patient outside of this window. This can help reduce alert fatigue by stopping alerts on patients for which AKI is presumably already well-known.

We are also aware that repeated alerting may lead to variable "dosing" of the intervention. Because our prior study involved one alert per patient, a uniform intervention was guaranteed for all patients in the alert arm. Here, it is feasible for patients to experience different "doses" of the alert, dependent upon the duration of AKI, frequency and timing of EMR access, and provider response to the alerts. As such, this trial is best conceptualized as an attempt to measure the effectiveness of an alert protocol rather than of an individual alert *per se*.

Randomization

Simple randomization is achieved within the Epic EMR system using an internal random number rule. Randomization occurs the first time the patient's chart is opened by an eligible provider after an AKI-defining creatinine value has been reported into the EHR. If the patient has AKI according to KDIGO creatinine criteria, and if the patient meets all other inclusion and exclusion criteria, the patient is automatically enrolled and randomized. Once randomized into either arm, the patient remains in this arm for the duration of their hospital stay. Beyond the primary intervention, no further tests or procedures will be performed on subjects in this trial.

Though commonly used in clinical trials, a permuted block randomization method was not utilized as this EHR has neither the functionality to generate permuted block lists or to import external randomization lists. Allocation concealment is maintained as the alert process is completely automated and performed within the EHR. In addition, we chose not to randomize at the provider level because this was deemed infeasible; patients at the participating hospitals are cared for by multiple providers, who may change during the course of a patient's hospital stay. While cluster randomization is a commonly used strategy that could reduce the risk of contamination across study arms, this method was deemedinfeasible in this study given the limited number of clusterable entities (i.e. six hospitals). Ward-based clustering would not be feasible given the fact that physicians (especially consultants) see patients throughout a given hospital. Additionally, because our six study sites range from small community hospitals to larger tertiary care centers, it would be difficult to assess differences between study arms containing confounders arising from potentially vastly different patient and provider populations. Performing simple randomization at the patient level will allow for sub-analyses of alert efficacy independently at each hospital and in individual wards. Stepped-wedge clustering has also been increasingly used in the evaluation of interventions related to service delivery. This method allows for both inter- and intra-cluster comparisons. However, the effect across study arms is likely to be confounded by unanticipated temporal and seasonal trends. Further, it would be difficult for study investigators to remain blinded as the time of crossover would be known. Both study designs have inherently greater statistical complexity to account for intracluster correlation and reduced statistical efficiency that does not outweigh their advantages. Given these considerations, we believe that a simple randomization scheme would be best for our study

design, however, we do recognize that this does have important implications with regards to contamination (see below).

Blinding

Participants and the study team will be blinded to the intervention, though obviously care providers will be aware of treatment assignment.

Clinician Outreach

While the unit of randomization is the patient, clinicians may also be considered subjects of this research. We will engage in pre-trial and periodic outreach to all clinicians who may be exposed to this study, informing them of the nature of the study, the fact that it is a randomized trial, and that alerts do not fire for all patients with AKI. We will additionally inform them that limited data is being collected regarding provider behavior. The pre-trial education will occur in the form of short education presentations at group and departmental meetings given by either the study's principle investigator (a clinical nephrologist) or a study coordinator. The study coordinator will also be at each site when the alerts become active in order to provide further provider education and answer any questions. Periodic site visits by the study coordinator or check-ins with local site investigators will occur on a monthly basis at each site to ensure that the alerts are functioning correctly and to reeducate any new providers on the floors. While we believe clinician education is important, we feel it's best that this process remain relatively simple to allow for broader adoption in the future should alerting prove beneficial. Further, the

alert pop-up contains methods to contact the study team. Most notable, if "disagree" is clicked, a free-text box is opened that allows providers to communicate their concern directly to the team. While piloting the popup in pre-trial activities, we used these responses to further tailor the language of the alert. We will also make it clear that data subject to clinician behavior (such as AKI documentation) will NOT be linked to individual clinicians.

Primary Outcome

The primary outcome will be a composite of progression to a higher stage of AKI, inpatient dialysis and inpatient death within 14 days of randomization, chosen such that we can objectively measure hard clinical outcomes of AKI that can be easily extracted from the EHR. Severity of AKI is strongly associated to longer-term outcomes, such as Chronic Kidney Disease (CKD) and End-Stage Kidney Disease (ESKD), while dialysis and death allow us to capture events that limit the rise in creatinine and that, if not accounted for, would potentially lead to missed cases of severe AKI. We chose this time frame for outcome assessment as the effect of an AKI alert might be diluted over time as more issues arise during the hospitalization. However, we also recognize that this time frame will potentially capture outcomes that occur in a period of time representing Acute Kidney Disease (AKD), a period of continued kidney dysfunction after AKI.[15]

Secondary outcomes of interest

Secondary outcomes of interest are listed in Table 2. Many of these are process measures, as we are particularly interested in measures that may change as a result of AKI alerts. In determining secondary outcomes of interest, we needed to balance outcomes that would be of interest to clinicians and other care providers with the feasibility of accurately determining those specific outcomes. This was particularly relevant for "best practices" such as dose-adjustment for medications, which can be somewhat subjective and thus requires direct chart review for determination.

To operationalize our "duration of AKI" endpoint, we define "C1" as the AKI-defining creatinine, and "C0" as the lowest preceding creatinine in the past 48 hours or past seven days depending on which KDIGO AKI criteria was met. For those defined by both, C0 will be the lower of the two creatinine values. Cessation of AKI will occur when a subsequent creatinine measure is within 0.3 mg/dl or 50% of C0, again depending on the KDIGO AKI criteria initially met (and within both if both criteria were met). While C0 may not represent true "normal" kidney function for a patient, selecting this time point avoids imputation of a baseline while avoiding potentially artificially prolonged AKI duration. Further, as it is conceivable that patients can be discharged prior to recovery and receive no follow-up creatinine measurements, we will evaluate differences in duration of AKI through the use of Kaplan-Meier estimators, allowing for censoring at death or discharge.

Table 2: Secondary outcomes of interest

ENDPOINT AND DEFINITIONS	DATA SOURCE
Mortality outcomes	

Inpatient mortality	Hospital record
Dialysis outcomes	
Inpatient dialysis	Order entry system
Discharged on dialysis	Social work records
Renal Failure Outcomes	
Percent who progress to Stage 2 AKI	Laboratory values
Percent who progress to Stage 3 AKI	Laboratory values
Duration of AKI	Laboratory values
Readmission Rate and Costs	
30-day readmission rate	Hospital record
Cost of index hospitalization	Billing records
Individual "Best Practice" Outcomes (proportion achieved per patient in study arm during index hospitalization)	
Contrast administration	Order entry system
Fluid administration	Order entry system
Aminoglycoside administration	Order entry system
NSAID administration/cessation	Order entry system
ACE inhibitor administration/cessation	Order entry system
Urinalysis order	Order entry system
Documentation of AKI	Post-discharge ICD-10 codes
Monitoring of creatinine	Order entry system
Monitoring of urine output	Hospital Record

Renal consult	Direct chart review
Provider awareness outcomes	
Chart documentation of AKI (by post-discharge ICD-10 codes)	Billing records
Chart documentation of AKI (adjudicated)	Direct chart review

AKI: acute kidney injury; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin converting enzyme

Subgroup analysis

The effect of the alert may differ based on several patient characteristics. We have therefore pre-specified several sub-groups of interest that are outlined in Table 3 and that will be considered hypothesis-generating for the future design of targeted alerts towards populations that are more likely to benefit from an alert system. Additionally, because we are enrolling patients across six hospitals that vary in size, type, and patient population, we will perform an exploratory analysis to determine the efficacy of alerts independently at each site. This analysis will employ logistic regression with a site-by-randomization interaction term to allow for simultaneous assessment of site-by-site baseline event rates and the site-by-site effect of AKI alerts.

Table 3: Planned subgroup analyses and justification

Subgroup of primary interest	**Justification**

Surgical patients (defined by admission to a surgical team)	Risk of under-documentation (reference)
Subjects with baseline creatinine <1.0mg/dl	AKI occurs when creatinine in "normal range"
Subjects with baseline creatinine <0.5mg/dl	AKI occurs when creatinine in "normal range"
Females	Lower rate of creatinine increase after AKI (reference)
African Americans	Higher rate of creatinine increase after AKI (reference)
Elderly (age >65, age >70 and age >75)	Lower rate of creatinine increase after AKI (reference)
Subjects in an ICU at the time of the alert	AKI may be overlooked in the setting of multiple clinical problems
Subjects who enter the study based on a 50% increase in creatinine vs. a 0.3mg/dl increase in creatinine vs both	Clinicians may be less likely to recognize a 0.3mg/dL change vs a 50% change

Contamination

As providers are not randomized and will be aware of patients who are randomized to the experimental arm, there is a risk of contamination of the intervention. Providers may use the

information provided in the AKI alert (i.e. definition of AKI, best practices with respect to AKI care, etc.) to improve their ability to detect AKI in patients not randomized to the experimental arm. In addition, improved knowledge with respect to the definition of an acute kidney injury and its appropriate management may improve the ability to detect AKI over time. In order to address this issue, we will examine the outcome rate in the control arm over time; if the outcome rate in the control arm improves over time, this may suggest contamination.

Beyond that, we will establish a pre-trial baseline cohort of patients that would be enrolled were the trial actively recruiting by retrospectively collecting a year's worth of pre-trial patient data from each study site. While temporal shifts in treatment may change outcomes over time independent of alerting, a significant improvement in AKI outcomes in the control arm of the trial vs. the pre-trial cohort would further suggest contamination.

Finally, it is possible that providers exposed to alerts may actually be at risk of increased *inattention* to AKI in patients of the control arm, as they may become accustomed or dependent upon receiving an alert as recognition of AKI. We will attempt to mitigate this through periodic outreach to clinicians and explicitly stating on the alert that not all patients with AKI trigger an alert.

Statistical Analysis

The primary outcome will be analyzed as a simple combination of progression of AKI, dialysis, and death at 14 days after randomization or at discharge (whichever comes first). If any one of

these three elements is positive, the composite outcome will be considered positive. The primary analysis will utilize the intention to treat principle. The proportion of patients who experience the primary outcome in the intervention and control groups will be compared by the chi-square test with Mantel-Haenszel correction for the 6 study strata (by hospital). Statistical significance will be based on a two-sided p-value of <0.05. As all pre-specified secondary outcomes are categorical in nature, these will be similarly analyzed, using the chi-square test with Mantel-Haenszel correction. We will not be correcting for multiple testing, especially because many of our secondary outcomes are likely correlated, making a true Bonferoni correction overly conservative. Therefore, we consider these outcomes as hypothesis-generating only, and any significant findings should be further explored.

Power and sample size considerations

To estimate the sample size, we conducted a retrospective analysis of patients with AKI at 3 of the 6 study hospitals. The composite outcome of progression of AKI, dialysis, or death occurred in 24.5% of 29,027 individuals with AKI in this analysis. A 20% reduction in this proportion (to 19.6%) would be clinically meaningful. To that end, a sample size of 2512 in each arm achieves 90% power to detect a difference this large at a two-sided alpha of 0.05. This was calculated with the PASS software package version 13.0[16], using the continuity-corrected form of the Cochran-Mantel-Haenszel test to account for the 6 hospital strata.[17,18] This gives a total population of 5,025 individuals with AKI. We have elected to increase this number by 20% to account for potential contamination of the effect across study arms, leading to a final sample size of 6,030 individuals.[19] In addition to adequately powering for the primary clinical outcome, this

sample size will allow us to detect at least a 16% increase in the odds of more best practices being completed in the intervention group.

Interim Analysis

We plan to have one interim analysis at the mid-point of the trial when 50% of patients have been enrolled. The interim analysis will allow us to alter the sample size or stop the trial earlier for ethical considerations, unexpected adverse events or high efficacy. The trial will stop for declaring efficacy if the effect size is large. We will use the O'Brien and Fleming stopping rule to stop the trial at a p-value of 0.001 for efficacy.[20] Alerting harm will be also be assessed using the primary outcome, but the threshold for stopping the study will be greater, at a p-value of 0.005. The DSMB will be unblinded to the study outcomes for these assessments, but the study team will remain blinded throughout.

Pre-intervention data

Pilot in the Medical Intensive Care Unit (MICU)

Prior to the implementation of the electronic alert across all six hospital systems, we piloted the alert from 01/08/2018 to 02/08/2018 in the medical intensive care unit at Yale-Haven Hospital. The purpose of this pilot phase was to evaluate the appropriateness of alerting, to solicit feedback from providers, and to ensure that the electronic methods of data capture were valid. There were 77 patients randomized (37 to alert, and 40 to control). The alert fired a total of 2,355 times, a

median (IQR) of 48 (23- 89) alerts per patient. Of 509 providers eligible to receive alerts, 323 providers received at least one, with a median of 1 (0 – 9) alerts per eligible provider (Figure 2). The median number of providers per patient was 17 (9-24), which may explain the low number of alerts seen per provider despite a high total number of alerts fired. The maximum number of alerts received by a single provider over the 30 days of the pilot was 78 alerts from 12 different patients. That provider was an acute care nurse practitioner assigned to the MICU for the duration of the pilot. Median alert duration was 0.84 (0.47-1.64 days (Figure 3). [Insert Figure 3.]

Outcomes for all randomized patients were as expected for a medical intensive care unit population. Inpatient death occurred in 29 (37%) of patients, while 4 (5.1%) were discharged home. The remainder of patients were discharged to a nursing facility, hospice, or transferred to another medical facility. In terms of AKI outcomes, the majority of these patients (52%) never had progression of AKI, 29% progressed to stage 2, and 18% progressed to stage 3.

Several iterations to the alert were made over the course of the pilot in response to provider feedback and internal testing. These are summarized in Box 1:

Change	Motivation
Excluded patients with “deceased” status	Occasional alerting on patients who had recently died was ghoulish and unactionable
Modified language to make it clear that “agreeing” with alert suppresses future alerts for themselves only	Providers are eager to find ways to suppress alerts once they have been alerted

Extended the "prior dialysis" exclusion criterion to one year	Some chronic dialysis patients would initially lead to an alert
Excluded providers who cannot enter orders	AKI Order set is not useful for individuals (such as nurses, medical students) who are unauthorized to enter orders.

Box 1: Summary of changes made to alerting during the piloting of the alert system.

ETHICS AND DISSEMINATION

Ethical Issues

This study posed several ethical issues that are worthy of discussion. First, in order to efficiently proceed with the study, we obtained a waiver of informed consent. United States federal guidelines require that in order to obtain a waiver of consent, 1) the research pose no more than minimal risk to the subject, 2) the waiver not adversely affect the rights and welfare of the subject, 3) the research could not be practicably carried out without a waiver and 4) whenever appropriate, the subjects be provided with additional pertinent information after participation. We felt that our study met all of the criteria noted above to qualify for a waiver of informed consent.

Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. We do not feel that post-facto informing of patients randomized in this trial is appropriate for several reasons. First, there is no guideline-based specific follow-up or intervention for acute kidney injury. Second,

many patients may incorrectly assume that acute kidney injury is an iatrogenic condition, caused by poor medical care, when this is not always the case and, rather, their AKI is indicative of the severity of the underlying medical condition. Finally, most patients will not be familiar with "acute kidney injury" and informing them of the presence of the condition may engender significant stress or anxiety without offering a tangible benefit. Because the intervention (alert) is a tool to make a provider aware of information already obtainable from the EHR, it is at the discretion of the provider to inform the patient of any relevant information regarding their AKI diagnosis, severity, and prognosis. We believe that the determination of the clinical impact and significance of AKI for a given patient rests with the primary providers and trust that they will act ethically with regards to the disclosure of the relevant medical information.

Prior to pursuing a waiver of informed consent, however, we weighed the issues of patient autonomy with the feasibility of actually obtaining consent from each patient. In order to obtain consent, we would need to either rapidly enroll all patients with an AKI at the moment of their AKI occurrence or prospectively inform all patients about the possibility of developing an AKI so that they would have already been consented at the moment of their AKI occurrence. The former method would be inefficient and utilize significant time and effort by study personnel, as about 10% of all hospitalized patients experience AKI. The latter method would risk loss of confidentiality for a significant number of hospitalized patients, ~90% of which will never go on to develop AKI. In addition, informing patients about the presence of an AKI will act as a separate alert of sorts, as patients in the control arm may inadvertently relay this information to providers or be placed in the position of withholding information to providers (in both the control and experimental arms), which may undermine the physician-patient relationship.

We also felt that the harm to patients with a waiver of informed consent will be minimal, as informing providers of the presence of an AKI is a low-risk intervention relying on a novel presentation of data that is theoretically already available.

Data Dissemination

As we recognize the novel strategies and potential impact of our trial, we are committed to the open and timely dissemination of our data. Our trial has been registered with clinical trials.gov (NCT02753751) and will be continually reviewed and updated. We intend to submit the results of our trial no later than one year following the completion date, and will include aggregate-level primary and secondary outcomes, participant demographics, statistical analyses and any adverse events. We also intend to disseminate information through publications and through the submission of our results the NIH data sharing repository.

Discussion

Acute kidney injury significantly increases the risk of morbidity and mortality in hospitalized patients. We designed a multi-center, randomized, controlled trial to determine whether the use of an AKI alert system will improve outcomes with regards to patients with this condition. The design of this trial was challenging for several reasons, presented above and summarized here. First, we needed to create a novel electronic alert system specific to this clinical trial; to do this, we needed to work within the limitations of the Epic electronic medical record system. Second,

the choice of a composite outcome of progression to AKI, inpatient dialysis, and inpatient death within 14 days of randomization was carefully chosen. Our process outcomes were carefully chosen as well, with a balance between utility of the best practice outcome and feasibility of measurement. Finally, the ethical issues associated with a lack of informed consent were carefully considered.

Randomized trials are of utmost importance to prevent implementation of alert systems that not only lack any demonstrable benefits on clinician behavior or patient outcomes but may also precipitate unforeseen consequences or burdens on the healthcare system.[21] The potential utility of an alert system is complicated by a variety of patient- and provider-specific factors that must be considered before its implementation. Positive outcomes on clinical efficacy should be weighed against potential risks. As an example, one frequently documented phenomenon, alert fatigue, is a decreased attention to alerts due to frequent or overabundant alerting.[22-24] This may not only lead to lack of efficacy in the studied alert, but it can negatively impact pre-existing alerts once deemed successful. Further, as alert override from physicians is a common problem of current alerting systems, careful thought must be put into design and implementation of the alert so as to create elements that are likely to increase provider adherence and thus improve alert success.[25-29] User feedback and positive user perception of the benefits of alerting are critical in creating successful alert systems that are well-received by providers.[30,31]

In conclusion, through a reiterative process of design, implementation, and testing, we have developed an autonomous AKI alert coupled to an automated trial screening, enrollment, and randomization engine. This approach decreases the costs of such a trial dramatically, while

simultaneously increasing generalizability (as virtually all eligible patients are enrolled). While this approach is not feasible for all clinical trials, especially those utilizing novel therapeutics, it is an ideal system to rigorously study systems-based interventions.

Authors' Contributions

Substantial contributions to the conception or design of the study: HIF, AG, NG, SL, HL, PMP, CRP, FPW

Acquisition, analysis, or interpretation of data: MM, YY, AB, BE, HIF, AG, SL, HL, PMP, CRP, EM, FPW

Drafting or revising the work critically: MM, MM, YY, AB, BE, HIF, AG, NG, SL, HL, PMP, CRP, EM, UU, FPW

Final approval of the draft to be published: MM, MM, YY, AB, BE, HIF, AG, NG, SL, HL, PMP, CRP, EM, UU, FPW

Agreement to be accountable for all aspects of the work and ensuring that questions related to accuracy or integrity are appropriately investigated and resolved: MM, MM, YY, AB, BE, HIF, AG, NG, SL, HL, PMP, CRP, EM, UU, FPW

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Ethics Approval

This work was approved by the Yale Institutional Review Board with a waiver of informed consent (IRB Protocol ID 1604017596) for Yale New Haven Hospital York Street Campus, Yale New Haven Hospital St. Raphael's Campus. Approval for the remainder of the sites was given by the Bridgeport Hospital Institutional Review Board with a waiver of informed consent.

Bridgeport Hospital is listed under IRB #041801. Lawrence and Memorial Hospital is listed under IRB #051802. Westerly Hospital is listed under IRB #071808.

Transparency Statement

The lead author (FPW) affirms that this manuscript represents an honest, accurate, transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned and registered have been explained.

Figure Legends:

Figure 1: The "pop-up" electronic alert. The alert gives relevant information regarding recent creatinine values and provides access to an AKI order set as well as relevant trial information.

Figure 2: AKI order set. This order set can be opened directly from the electronic alert and contains generic options for further work-up.

Figure 3: Histogram demonstrating the number of alerts received by providers during the pilot phase.

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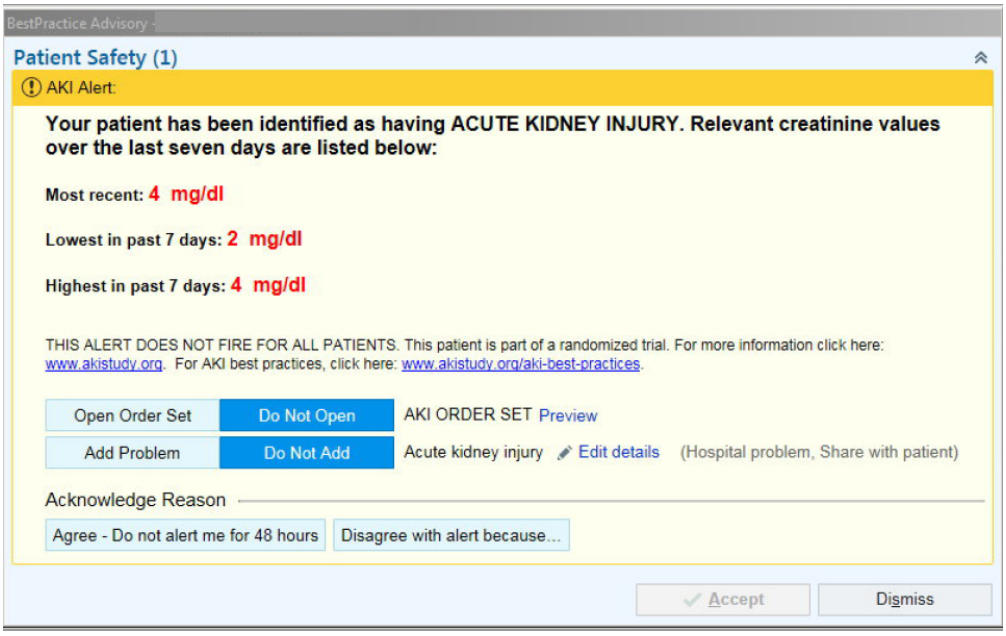


The "pop-up" electronic alert. The alert gives relevant information regarding recent creatinine values and provides access to an AKI order set as well as relevant trial information.

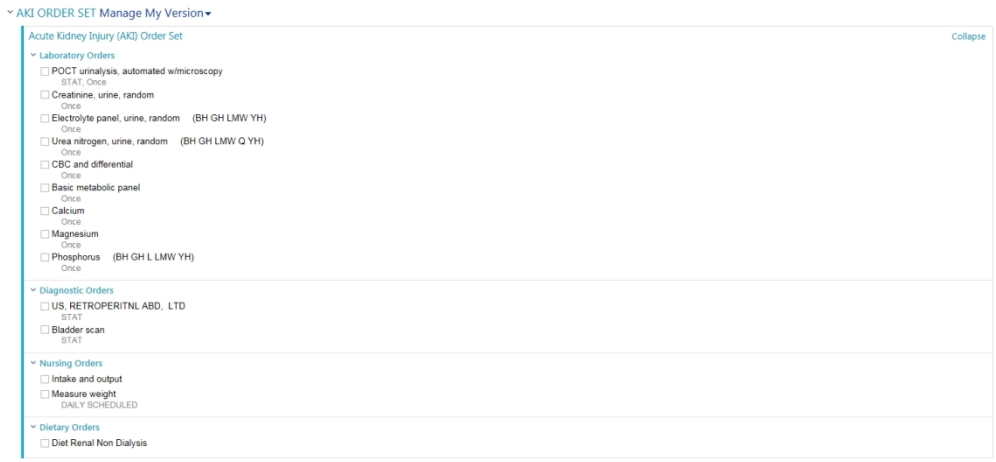
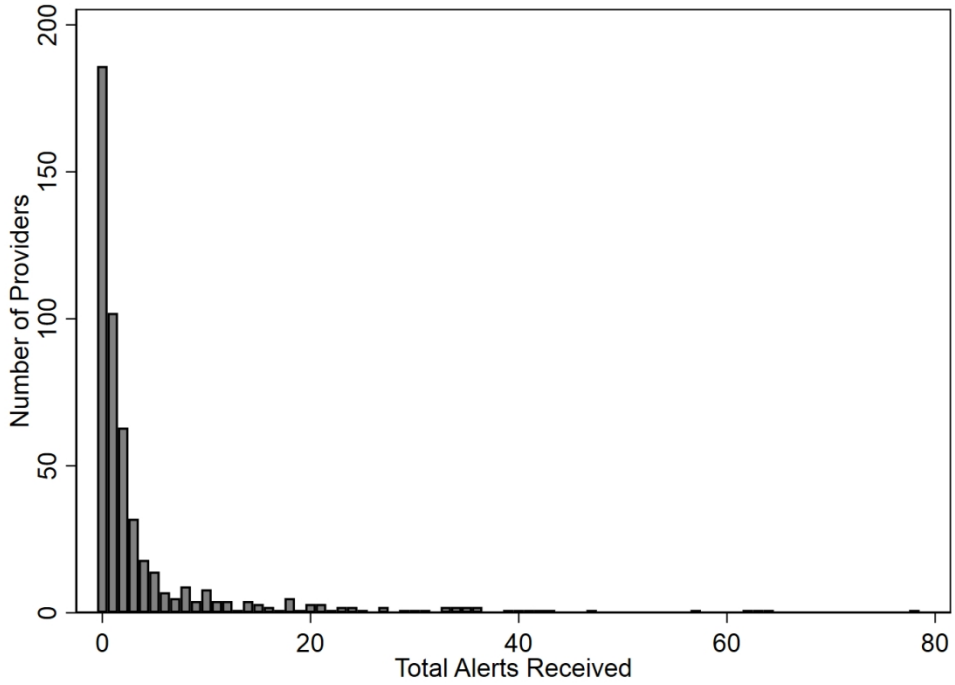


Figure 2: AKI order set. This order set can be opened directly from the electronic alert and contains generic options for further work-up.



Histogram demonstrating the number of alerts received by providers during the pilot phase.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	Supplemental Material
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 24

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Supplemental Material
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A no comparators being used other than usual care
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	8

		applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A subjects are unaware of their participation in the trial and do not require adherence
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A done solely electronically via EMR
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Supplemental Material

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A Patients are blinded and cannot discontinue intervention
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplemental Material
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplemental Material
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported	Supplemental Material

		adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplemental Material
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Supplemental Material
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A This trial has a waiver of informed consent
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplemental Material
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplemental Material
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants,	23

		healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Supplemental Material
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Supplemental Material
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a