Electronic Alerts for Acute Kidney Injury Amelioration (ELAIA-1)
NCT Title and ID: Optimizing Electronic Alerts for Acute Kidney Injury
NCT02753751
April 24, 2020

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

This study is designed to determine whether automated, electronic alerts for Acute Kidney Injury (AKI) will be effective at reducing progression of AKI, inpatient dialysis, and inpatient mortality rates in a hospitalized population.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Acute kidney injury (AKI) carries a significant, independent risk of mortality among hospitalized patients [1,2]. Recent studies have demonstrated increased mortality among patients with even small increases in serum creatinine concentration [3,4]. 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[5]. Early nephrologist involvement may also improve outcomes in AKI[6]. Without appropriate provider recognition of AKI, however, none of these measures can be taken, and patient outcomes may suffer. AKI is frequently overlooked by clinicians[7], but carries a substantial cost, morbidity and mortality burden.

Our research group conducted a pilot, randomized trial of electronic alerts for acute kidney injury in 2014.[8] The trial, which randomized 2400 patients with AKI as defined by an increase in creatinine of 0.3mg/dl over 48 hours or 50% over 7 days, found that alerting physicians to the presence of AKI did not improve the course of acute kidney injury, reduce dialysis or death rates. Our pilot study demonstrates that there is clinical equipoise regarding the effectiveness of alerting, and that alerting to the presence of this condition (which does not have a treatment) is not standard of care.

Our pilot study was conducted in a single hospital, and the alert itself did not describe specific actions that a provider could take. In the present proposal, we seek to expand upon our prior study to determine if the use of an electronic alert will improve best practices for the care of hospitalized patients with AKI and/or improve rates of progression of AKI, dialysis or mortality in hospitalized patients across multiple hospital centers.

We propose a randomized, controlled trial of an electronic AKI alert system. Using the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria, inpatients at six hospitals, including Yale New Haven Hospital, YNH – St. Raphael Campus, and Bridgeport hospital, will be randomized to usual care versus an electronic alert informing providers of the presence of AKI and providing them with an AKI order set for management of AKI. The form of the electronic alerts (including the information contained in the alert) is described in detail in the research plan. The primary outcome will be a composite of progression of acute kidney injury, dialysis and death within 14 days of randomization. Secondary outcomes would focus on the efficient delivery of care and include length of stay, ICU utilization, rate of acute dialysis, 30-day readmission rate, and a variety of process of care variables.

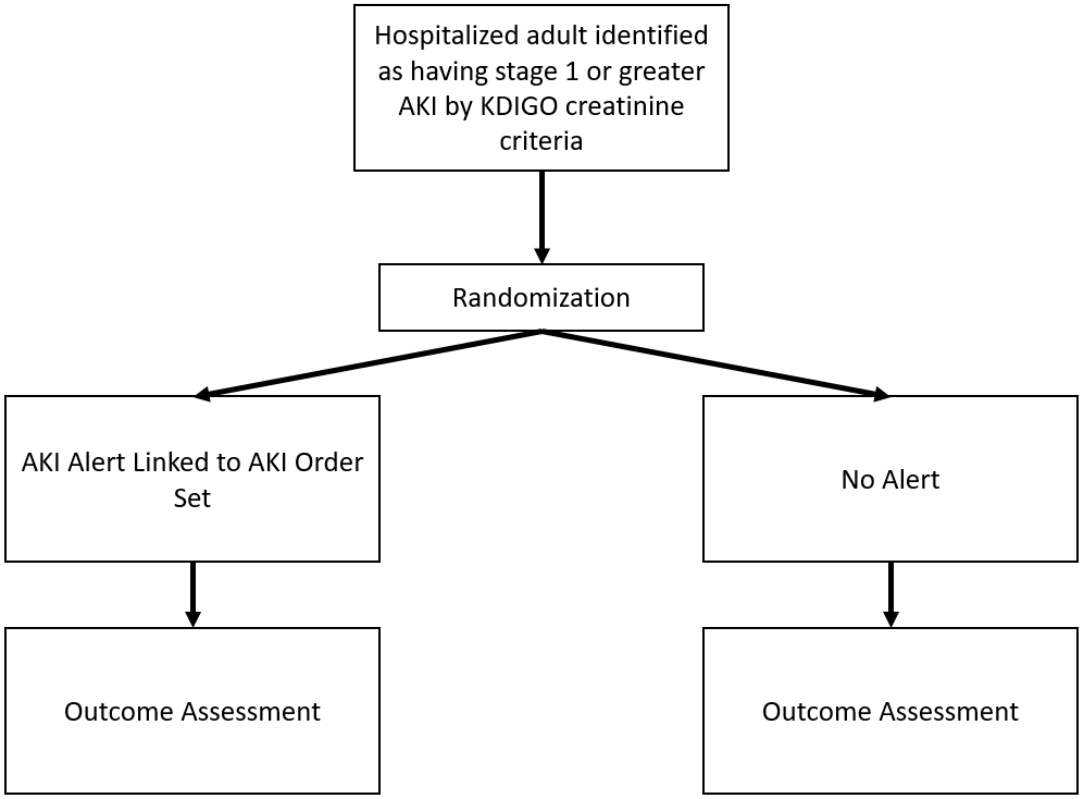
3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and**

include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

General Design

This is a randomized, single-blind intervention trial of an electronic alert coupled to an AKI order set versus standard care among patients with AKI.

Study Flow Diagram:



Subject participation will be limited to the duration of hospitalization.

Subject Selection and Withdrawal

Inclusion Criteria
1. Adults ≥18 years admitted to a participating hospital.
2. Acute kidney injury as defined by KDIGO creatinine criteria
   -0.3mg/dl increase in inpatient serum creatinine over 48 hours OR
   -50% relative increase in inpatient serum creatinine over 168 hours.

Exclusion Criteria

1. Dialysis order prior to AKI onset
2. Initial creatinine ≥ 4.0mg/dl
3. Prior admission in which patient was randomized
4. Admission to hospice service or comfort measures only order
5. ESKD diagnosis code
6. Kidney transplant within six months

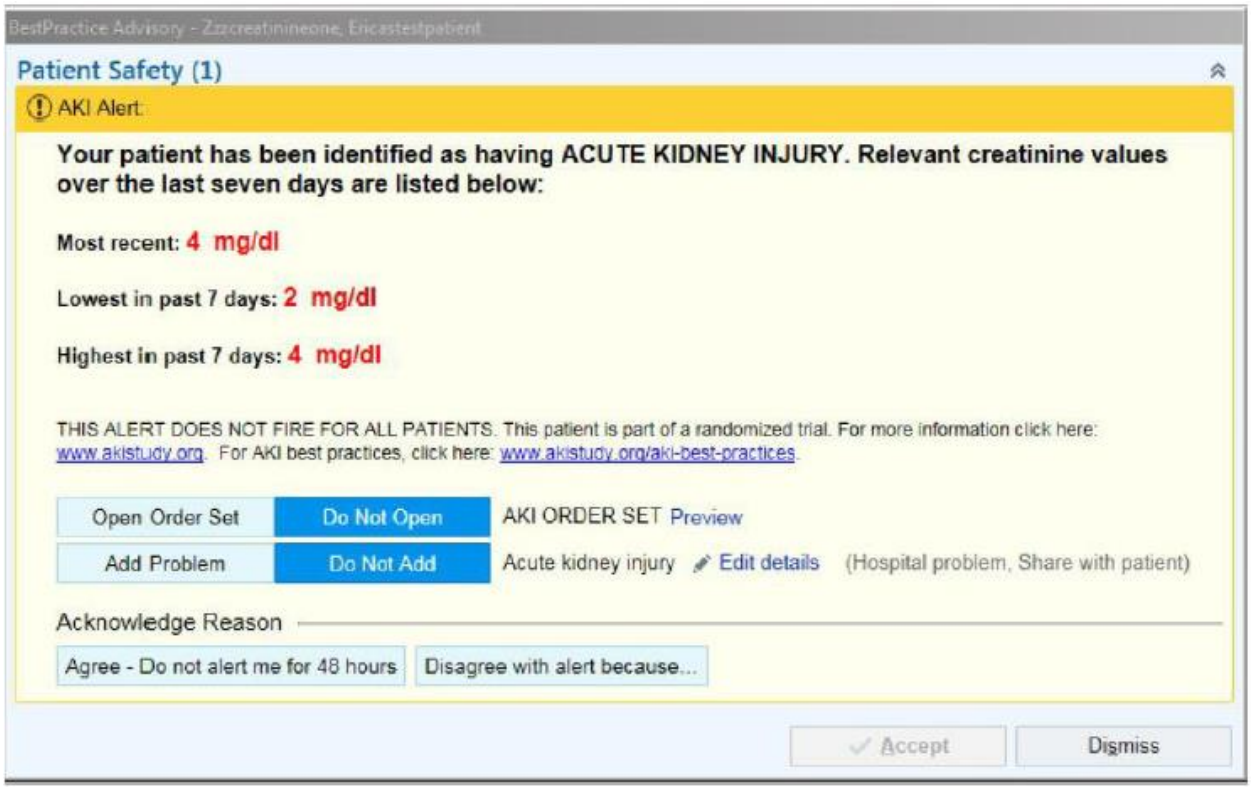
Subject Recruitment and Screening
Due to the nature of this research, subjects will be recruited when electronically identified by the presence of a rising serum creatinine concentration as defined by the inclusion criteria.

Identification of subjects will be performed within the EPIC system, using a best-practice alert build developed by the Joint Data Analytics Team (JDAT) at Yale. The build will examine the most recent creatinine value, and compare it to the minimum value in the past 48 hours and 7 days. If the current value is 0.3mg/dl above the 48-hour minimum, or 50% higher than the 7-day minimum, the patient is defined as having AKI and he or she will be randomized as part of this trial. We have secured enthusiastic agreements from both JDAT and the Best Practice Alerts committee to engage in this line of research.

As this is an intervention assessing the influence of an alert system on provider behaviors surrounding AKI, we cannot inform patients of their participation in the study at the time of enrollment, as this would contaminate the randomized exposure.

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. However, we will also make it clear that data subject to clinician behavior (such as AKI documentation) will NOT be linked to individual clinicians. All such data will only be analyzed in aggregate.

Intervention
Description
Patients randomized to the intervention will have an alert generated within the electronic health record, which will consist of a "pop-up" within the EMR when the provider assesses a patient record after the AKI-defining creatinine value has been registered. Providers who receive an alert include physicians, physician assistants, nurse practitioners, advanced practice registered nurses, fellows, physician/anesthesiologists, physician/sedation specialists, and residents. These alerts will be built by JDAT, who, as mentioned, have agreed to aid in the development of this study. The alert text will be displayed as follows:



Intervention Duration

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

- The provider acknowledges the alert by "agreeing" that AKI is present (alert will be suppressed for 48 hours
- The most recent creatinine does not meet AKI criteria
- The patient receives an order for hemodialysis, continuous renal replacement therapy, or peritoneal dialysis
- The patient is transferred to the hospice service
- The patient is discharged from the hospital

Method for Assigning Subjects to Intervention Randomization will occur the moment AKI is detected by the electronic monitoring system within the EPIC best practice alert framework, as developed by JDAT. Randomization is achieved within the Epic system using a random number rule that is incorporated in the alert. This ensures that, upon meeting criteria, each patient is immediately and randomly assigned to an arm. Logic checks within the alerts ensure that once a patient is assigned to an arm, they remain on that arm for the remainder of their hospital stay.

Prior and Concomitant Therapy

Potential subjects will be excluded if they have a prior order for dialysis. Beyond that, all therapies are permissible within this protocol.

Blinding of Intervention
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.

All investigators will be blinded to treatment assignment until the end of the trial period. Care providers will, obviously, not be blinded to the intervention as they are receiving the alert. We will engage in both pre-trial and periodic teaching and discussion with all care providers (administered through short presentations at divisional conferences) to inform clinicians about the nature of the study, the fact that alerts do not fire for all patients with AKI, and to discuss specific factors that are being measured.

Primary Study Endpoints
Primary Outcome: The primary outcome will be a composite of progression to a higher stage of acute kidney injury (a doubling or tripling of creatinine from the pre-alert baseline), inpatient dialysis, or inpatient death at within 14 days of randomization.
-For patients who are discharged, we will impute 14-day creatinine using the last observation carried forward method.

Secondary Study Endpoints
1) Mortality Outcomes
-14-day mortality
-Inpatient mortality

2) Dialysis outcomes
-14-day dialysis
-Inpatient dialysis
-Discharge on dialysis

3) Renal Failure Outcomes
-Percent who progress to stage 2 AKI
-Percent who progress to stage 3 AKI
-Duration of AKI

4) Readmission Rate and Costs
- 30-day readmission rate
- Cost of index hospitalization

5) Individual "Best Practice" Outcomes, proportion achieved per patient in study arm during index hospitalization
- Contrast administration
- Fluid administration
- Aminoglycoside administration
- NSAID administration / cessation
- ACE inhibitor administration / cessation
- Urinalysis order
- Documentation of AKI
- Monitoring of creatinine
- Monitoring of urine output
- Renal consult

6) Provider awareness outcomes
- Chart documentation of AKI (by post-discharge ICD-10 codes)
- Chart documentation of AKI (adjudicated)

Study Procedures

Randomization

Randomization will occur the moment AKI is detected by the electronic monitoring system within the EPIC best practice alert framework, as developed by JDAT. Beyond the primary intervention, no further tests or procedures will be performed on subjects in this trial. Randomization will be performed within the Epic system using a random number rule that is incorporated in the alert. This ensures that, upon meeting criteria, each patient is immediately and randomly assigned to an arm. Logic checks within the alerts ensure that once a patient is assigned to an arm, they remain on that arm for the remainder of their hospital stay.

Fourteen days post-randomization

Primary endpoint ascertainment

Thirty days post-randomization

Secondary endpoint ascertainment

Statistical Plan

Sample Size Determination

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In our retrospective analysis of patients with AKI at 3 potential study hospitals, the composite outcome of death, dialysis, and progression of AKI was 24.5% (of 29,027 individuals with AKI). We believe a clinically meaningful relative reduction in this risk would be 20%, leading to an absolute rate of 19.6% in the intervention group. By enrolling 5,024 patients (2,512 in each group), we would have 90% power to detect a difference in outcome at least this extreme at a two-sided alpha of 0.05 as calculated using the Cochran-Mantel-Haenszel test (accounting for 6 hospital strata). 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. This sample size will also allow us to detect at least a 16% increase in best practices measures in the intervention group.

We must also consider that patients enrolled once in the trial will be excluded from enrolling again (on another admission, for example). While we don't have data on the rates of recurrent AKI we estimate that up to 20% of eligible patients may be excluded on this basis, which may slow recruitment somewhat.

In addition, pauses in trial enrollment may occur due to protocol changes / amendments based on feedback from providers and for quality improvement activities.

As such, we expect active enrollment, data acquisition, and outcome assessment to be completed over a three-year period.

Statistical Methods

The primary analysis will utilize the intention to treat principle. The primary outcome (a composite of progression of AKI, dialysis, and death) will be compared across the groups using the Mantel-Haenszel chi-square test for correction for the 6 study strata (by hospital). Statistical significance will be based on a p-value of <0.05.

In addition, a retrospective examination will be performed to assess improvement in the control group before / after intervention as a measurement of contamination. We expect that providers who receive AKI alerts on some patients may be more likely to look for AKI in other patients, potentially diluting the effect of the intervention – this pre/post intervention analysis will help in assessing that level of contamination.

Because we are enrolling patients across six sites, we will do an exploratory analysis to determine the efficacy of alerts independently at each hospital.

We have specified several subgroups in whom the benefit of an AKI alert may differ from the general population. These groups will be analyzed as secondary and exploratory analyses. They include:

- -Surgical patients
- -Subjects with baseline creatinine <1.0mg/dl
- -Subjects with baseline creatinine <0.5 mg/dl
- -Females (due to lower rate of increase in creatinine after AKI)
- -African Americans (due to higher rate of increase in creatinine after AKI)
- -Elderly subjects (age > 65, age > 70, and age > 75)
- -Subjects in an ICU at the time of the alert
- -Subjects who enter the study based on relative vs. absolute creatinine criteria vs. both

Finally, as the academic year progresses, new clinicians (such as residents and interns) may become more facile in their ability to recognize AKI, which may attenuate the effect of this intervention. We will model this in exploratory analyses using an intervention-by-time of year interaction term in models of the primary outcome.

4. **Genetic Testing N/A** ☒
   A. Describe
      i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
      ii. the plan for the collection of material or the conditions under which material will be received
      iii. the types of information about the donor/individual contributors that will be entered into a database
      iv. the methods to uphold confidentiality

   B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
   C. Is widespread sharing of materials planned?
   D. When and under what conditions will materials be stripped of all identifiers?
   E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
      i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

   F. Describe the provisions for protection of participant privacy
   G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
   This study will enroll individuals of greater than or equal to 18 years of age admitted to one of the 6 participating hospitals, including Yale New Haven Hospital, St. Raphael's Hospital, Greenwich Hospital, Lawrence and Memorial Hospital, Westerly Hospital and Bridgeport hospital. As Greenwich hospital, Lawrence and Memorial Hospital, Westerly Hospital and Bridgeport Hospital have their own IRBs, we will apply to each of those IRBs for approval individually. , We will enroll only patients with acute kidney injury. Exclusion and inclusion criteria are described above.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses

☐ Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria
1. Adults >=18 years admitted to a participating hospital.
2. Acute kidney injury as defined by KDIGO creatinine criteria
   -0.3mg/dl increase in inpatient serum creatinine over 48 hours OR
   -50% relative increase in inpatient serum creatinine over 168 hours.

Exclusion Criteria
1. Dialysis order prior to AKI onset
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4. Admission to hospice service or comfort measures only order
5. ESKD diagnosis code
6. Kidney transplant within six months

8. How will **eligibility** be determined, and by whom?
   Eligibility will be determined by a computerized algorithm. All patients admitted to YNHH, and YNHH St. Raphael Campus will be assessed electronically for eligibility (without human intervention). This assessment is performed within the Epic best practice alert framework as built with JDAT. Those that meet the inclusion criteria and who have no exclusion criteria will be automatically enrolled.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

We consider the primary intervention (alerting of providers to the presence of a condition) to be minimal risk, however no intervention is risk free.

Risks of the generic AKI alert: Providers may be overly aggressive with diagnostic or therapeutic interventions if they are informed of the presence of Acute Kidney Injury. While we did not see this behavior in our pilot trial, we can imagine that providers who see an alert might give more fluids, or keep the patient in the hospital longer. Though, in our pilot study, there was no effect of the alert overall on rates of renal consult or dialysis, we did see a *higher* rate of renal consult and dialysis in the surgical ward subgroup, though this trend did not maintain statistical significance when adjusted for multiple comparisons.

Risks to providers: The primary risk to providers is annoyance and interruption in workflow due to the presence of alerts. Providers are, however, exposed to many alerts already in the usual flow of care. In fact, the evaluation of alerts in the clinical trial paradigm is actually vital to *reduce* the amount of alerts providers receive (by eliminating those that are ineffective).

General Risk of Alerting in the Trial Format: Not all patients with AKI will be randomized to alerting arms of this study. As such, providers may be less attentive to the presence of AKI in all patients. We mitigate this alert by including the phrase "THIS ALERT DOES NOT FIRE FOR ALL PATIENTS WITH AKI" at the end of every alert. In addition, prior to the onset of the study, our study team will engage in brief educational talks with all sections practicing in the hospitals of interest to inform them of the structure and function of the alert trial and indicate, again, that not all patients with AKI will receive an alert.

As with all studies where PHI is collected, loss of privacy is a risk for participants. We limit this risk through our use of an entirely-electronic data collection system and our data security plan outlined below.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

All patient data will be kept on a secure, HIPAA-compliant server with 2-factor authentication, accessible only from within the Yale firewall, or via VPN protocols, and only by study personnel. In addition, at the time of data acquisition, a unique study ID number will be assigned to each patient. All PHI will be linked to this study ID number in a database that is *separate and distinct* from the primary dataset which includes clinical information. This linking dataset will be maintained on a separate HIPAA-compliant server and will only be accessible by the study investigators.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

The protocol presents minimal risks to all subjects. If an unlikely adverse event should occur, it will be dealt with as outlined in response 11c.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

(N/A)

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html.

We have uploaded our Data and Safety Monitoring Plan with this Application.

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Statistical Methods
The primary analysis will utilize the intention to treat principle. The primary outcome (a composite of progression of AKI, dialysis, and death) will be compared across the groups using the Mantel-Haenszel chi-square test for correction for the 6 study strata (by hospital). Statistical significance will be based on a p-value of <0.05.

In addition, a retrospective examination will be performed to assess improvement in the control group before / after intervention as a measurement of contamination. We expect that providers who receive AKI alerts on some patients may be more likely to look for AKI in other patients, potentially diluting the effect of the intervention – this pre/post intervention analysis will help in assessing that level of contamination.

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1. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit. Care Med.* 2006;34(7):1913-1917.
2. Chertow GM, Soroko SH, Paganini EP, et al. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. *Kidney Int.* 2006;70(6):1120-1126.
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