2020

# IMPROVE AKI Cluster-Randomized Trial (IMPROVE-AKI)

NCT03556293

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**IMPROVE AKI: A Cluster-Randomized Trial of Team-Based Coaching Interventions to IMPROVE Acute Kidney Injury**

***Objective:***

We propose to test the implementation of evidence-based preventive interventions through a Virtual Learning Collaborative (VLC) with and without the novel use Automated Surveillance Reporting (ASR) intervention to change clinical practice and improve patient safety in common diagnostic procedures. We focus this test on prevention of acute kidney injury (AKI) following diagnostic or interventional cardiac catheterization (herein referred to as "*procedure*").[6] Over 2 million people in the United States undergo this procedure each year. AKI, a patient safety metric set by the National Quality Forum, occurs in up to 14% of all patients following a procedure and up to 50% in patients with pre-existing chronic kidney disease (CKD)[1] making AKI this procedure's most prevalent adverse event.[2,3,7] When AKI occurs, patients have an increased risk of cardiovascular events, prolonged hospitalization, end-stage renal disease, and mortality.[8] We have shown the inconsistent application of standardizing orders, using adequate oral and IV fluids, and limiting contrast dye dose is responsible for a five-fold variability in the incidence of post-procedure AKI across hospitals.[1,9,10]

Our group and others have contributed to an evidence-based of widely accepted interventions to prevent AKI in patients undergoing cardiac catheterization.[1,3,11-13] These interventions, however, are rarely implemented, leaving many patients at risk.[1] The critical research question is not what hospitals should do, but how to get them to do it. Our own work has demonstrated the feasibility and potential effectiveness of two promising implementation strategies to increase the use of AKI prevention protocols: 1. Virtual Learning Collaborative (VLC) to support the use of an AKI Prevention Toolkit showing a statistically significant 28% reduction in AKI (piloted in a 10-hospital trial: AHRQ grant HS018443), and 2. Automated Surveillance Reporting (ASR) providing near-realtime feedback to frontline care workers (VA HSRD grant IIR11292).[1,7,14]

The proposed study asks whether supporting the use of the AKI Prevention Toolkit by 1) VLC coaching augmented by ASR (VLC+ASR) will lead to better patient outcomes compared to TA, TA + ASR, and VLC alone; and 2) VLC will be superior to TA with or without ASR. We will address these questions in a 2x2 factorial cluster-randomized trial that randomizes 16 hospitals to receive one of the following interventions for 18-months: A) Technical Assistance (TA); B) Technical Assistance with Automated Surveillance Reporting (TA+ASR); C) Virtual Learning Collaborative (VLC) with team-based coaching; and D) Virtual Learning Collaborative with Automated Surveillance Reporting (VLC+ASR). All sites have been recruited and will receive the AKI Prevention Toolkit (Appendix 1) that includes 3 core preventive interventions: 1. Standardized order sets; 2. IV and oral fluids; and 3. Reduced contrast volume. The interventions were developed and tested in our pilot to implement AKI preventive strategies.[1,3]

***Specific Aims***

**Specific Aim 1: Compare the efficacy of a Virtual Learning Collaborative and/or Automated Surveillance Reporting compared to Technical Assistance to reduce the incidence of AKI.**

Our *working hypothesis* is that multi-disciplinary clinical teams in a Virtual Learning Collaborative (VLC) with team-based coaching in process measurement and implementation methods will reduce the incidence of AKI following procedures, compared to a Technical Assistance (TA) intervention, both with or without Automated Surveillance Reporting (ASR). We also hypothesize that ASR will have a bigger impact with VLC than with TA.

**Specific Aim 2: Evaluate the sustained efficacy of Virtual Learning Collaborative and/or Automated Surveillance Reporting to reduce the incidence of AKI following the intervention period.**

Our *working hypothesis* is that VLC coaching augmented by ASR (VLC+ASR) will be superior to TA, TA +ASR, and VLC alone. Secondarily, VLC will be superior to TA with or without ASR. Sixteen hospitals will continue to enroll patients following the 18-month intervention period for an additional 18-months post-intervention with the TA, ASR, and VLC interventions removed. We will evaluate whether the reduced incidence of AKI will be sustained for each of the randomized clusters during the post-intervention phase.

Impact: Evidence of the efficacy of Virtual Learning Collaborative, augmented by Automated Surveillance Reporting, on the sustained use of preventive interventions will enable hospitals to improve quality of care for the over 2 million patients undergoing cardiac catheterization and, as a result, reduce their significant risk of acute kidney injury. More broadly, these findings will be relevant to supporting hospital's implementation of a wide array of preventive interventions and has the potential for vastly improving patient care and outcomes.

**Specific Aim 3: Laboratory Predictors of AKI in Patients Undergoing Coronary Angiography**

In th is aim, our goal is to examine whether lower serum magnesium, lower hemoglobin, higher hemoglobin A1c, and other laboratory predictors are associated with a higher risk of AKI in patients undergoing coronary angiography. We are defining AKI as a doubling of serum creatinine (SCr) or need for RRT. We will also examine whether laboratory predictors are associated with an increased risk of death at 30 days.

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**A. Background and Significance:**

Over two million diagnostic or interventional cardiac catheterization procedures are performed in the United States each year.[6,15] Acute kidney injury (AKI) is preventable but occurs in up to 14% of all patients following a procedure and up to 50% in patients with pre-existing chronic kidney disease (CKD),[1] making AKI one of the most prevalent adverse events.[2,3,7] Reducing the prevalence AKI is a patient safety objective set forth by the National Quality Forum.[16] When AKI occurs, patients have an increased risk of

cardiovascular events, prolonged hospitalization, end-stage renal disease, all-cause mortality, and increased acute care costs of over $7,500 per case.[8,11,17] Based on our preliminary evidence in our pilot demonstrating a statistically significant 28% reduction in AKI in patients with pre-existing CKD, we estimate that over 70,000 AKI events could be prevented with an annual cost savings of $525 million each year nationally using evidence based strategies delivered through a Virtual Learning Collaborative (VLC) in common diagnostic procedures using contrast dye.

Scientific Premise: The premise is that a parsimonious set of two evidence-based preventive interventions have been shown to substantially reduce the incidence of post-procedure AKI; however, these preventive interventions are applied inconsistently. We have strong preliminary evidence suggesting that more systematic application of these preventive interventions can dramatically reduce the complication of AKI and reduce costs. The scientific premise of this application rests on three assertions: 1) a parsimonious set of evidence-based preventive interventions are effective in preventing AKI, 2) these preventive interventions are applied inconsistently, among hospitals, and 3) our preliminary data from a large pilot of our interventions suggest AKI can be prevented. There are two widely accepted preventive interventions to prevent AKI after procedures: 1) standardizing orders for intravenous (IV) volume expansion, and 2) limiting contrast volume. For intravenous (IV) fluid administration, three prospective randomized trials in over 1,000 patients have compared giving fluid to no fluid.[18-20] These trials included procedures where the urgency to restore flow to an occluded coronary artery preempted the ability to administer IV fluids before contrast exposure. In all three trials, a significant reduction in the incidence of AKI was seen in those who received fluid compared to no fluid.[18-20]

With respect to the second premise, our preliminary data suggests the inconsistent application of AKI preventive interventions is responsible for five-fold variability in AKI incidence after cardiac catheterization.[1] We collected this evidence from a sample of 10 hospitals with interviews and data collection to ascertain the rate of AKI and determine the presence or absence of protocols for AKI prevention. Only one in five hospitals had established protocols for preventing AKI. Hospitals without established protocols were found to have significantly higher rates of AKI.[1] Since our evidence was limited to a regional collaborative, we validated our findings in a VA nationwide survey. The VA survey confirmed our findings, where only one in four hospitals with cardiac catheterization laboratories had a mandated IV fluid protocol for AKI prevention. Therefore, our objective is to increase the consistency with which AKI preventive approaches are applied, which was demonstrated by a 28% reduction in AKI in our preliminary data and pilot intervention described below.[3]

Figure 1

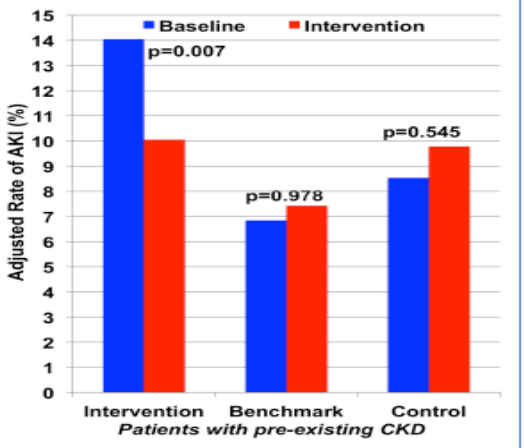



*Figure 1. Adjusted rates of AKI are plotted for baseline (blue) and the intervention (red) phases.*

With respect to the third premise, we tested a VLC coaching intervention that employed best-practice approaches to prevent AKI (HS018443). This pilot was a pre-post implementation design in 10 hospitals with 21,067 consecutive PCI patients (**Figure 1**), which included 4,131 patients with pre-existing CKD.[1,3] **We observed a 28% reduction in AKI for patients with pre-existing CKD** (≥Stage 3).[3] Strengths included multiple intervention hospitals, and a large sample, demonstrating a strong benefit of team-based coaching and bundling preventive strategies to prevent AKI. Therefore, we will build on our pilot to conduct a national cluster-randomized controlled trial.

**Aim 1. Supporting Literature.** AKI Prevention. Avoiding potentially nephrotoxic contrast volumes during cardiac catheterization is a target for AKI prevention.[11] The link between contrast volume and AKI has been well established.[21] The consistent application of reducing contrast volume and avoiding volumes exceeding the safe threshold is an essential protocol in our proposed interventions. There have been no randomized contrast dosing trials limiting contrast volume, yet limiting contrast is supported in the guideline.[13]

While it is known that IV volume expansion and reducing contrast dose are beneficial, these preventive measures for AKI are inconsistently applied.[1] To date, there have been no empirical evaluations; a logical next step would be to empirically evaluate implementation methodologies to prevent AKI in cluster-randomized control trials. Based on our pilot, we propose VLC and ASR to be the vehicles for the consistent application of AKI preventive strategies.

**Aim 1. Preliminary Data**. Virtual Learning Collaboratives (VLC). Despite widespread use and publication of learning collaboratives, such as the Institute for Healthcare's (IHI) Breakthrough Series in health care settings,[22,23] to our knowledge there are no studies testing the effectiveness of a plug-in automated surveillance reporting (ASR) intervention with or without a learning collaborative. Few randomized trials have evaluated learning collaboratives using quantitative outcomes.[24] According to a recent systematic review of 23 learning collaborative studies, only five used a controlled design, with only one RCT measuring quantitative outcomes; none compared effectiveness to an active control condition.[23] Research findings are also limited to studying face-to-face collaboratives,[23,24] which entail significant costs associated with travel, lodging, meals, and meeting facilities. A recent refinement is the VLC, conducted by video, phone, and e-mail, decreasing the cost of participation and increasing the speed of incorporating lessons into practice. There is limited but encouraging data on VLC effectiveness. A 2006 IHI study of a virtual collaborative to improve primary-care access achieved outcomes comparable to those of a traditional collaborative at a reduced cost.[25] A 2011 cluster-randomized trial assigned 60 hospitals to use either VLC (n=31) or a toolkit (n=29) for prevention of nosocomial infections.26 The VLC outpaced the toolkit in changing care processes, though neither approach improved outcomes. These reports suggest VLC may be effective but requires more testing.

**A.1. Critical need to test TA**. There is a critical need to evaluate the VLC and ASR interventions against TA alone to determine if the null hypothesis is supported that there is no difference in TA compared to more intensive interventions such as the VLC with or without ASR. If the null hypothesis is not supported, the AKI Prevention Toolkit could be rolled out nationally in a more rapid dissemination design compared to that of a national campaign involving a more robust VLC and/or ASR.

**A.2. Automated Surveillance Reporting (ASR**). The landmark prediction model for AKI was established by Mehran in 2004 on a large PCI cohort. However, the discrimination of the model was poor (c-statistic=0.67).[27] It is well known that models have degrading calibration performance over time and across different practice settings.[28,29] These prediction models have not yet been incorporated into surveillance systems that could provide real-time feedback to operators on both the risk of AKI and AKI incidence.[14] ASR is important and useful in detecting and understanding changes in performance. We are the first to develop an ASR toolkit for medical product comparative effectiveness and institutional and provider care variation detection,[30-33] and further adapted it to conduct surveillance for post-catheterization AKI in the VA health system (IIR11292). The toolkit uses the new VA AKI prediction model developed by the PIs[14] and provides tailored automated reports to VA operators on AKI outcomes to provide teams with near-real-time data on AKI outcomes and consistent adoption of protocols. ASR can be used to identify problems, encourage the need for improvement, and quantify the extent to which improvement initiatives have been successful.[34] It is well established by that participating in an outcome monitoring program can improve patient outcomes, provide clinicians with targeted data for improved decision-making, and lower costs of care.[35]

**A.3. Expertise in Virtual Learning Collaboratives (VLC).** In 2011, the VA National Center for Patient Safety (Zubkoff, R01MH102325) had initial success with the use of a VLC to reduce postoperative respiratory failure.[36] Learning sessions and presentations were held via teleconferences, and all materials were distributed using a listserv and collaborative website. One unique component of this VLC was the use of coaches to assist teams in making improvements. Coaches provided feedback to teams on monthly reports and held group calls to foster sharing and communication among teams. Over 6 months, teams attended calls and submitted monthly progress reports. Over 76% of team members attended all 11 calls; each team implemented an intervention; 44% implemented at least 4 unique evidence-based interventions, and 31% implemented at least 5 out of 11 interventions.[36] This project observed improved outcomes among participating teams suggesting the VLC is a useful improvement strategy. Zubkoff and colleagues have continued to conduct additional VLCs in the VA to prevent falls, hospital-acquired conditions, and pressure ulcers. Our research team is experienced in national VLC (Zubkoff, R01MH102325) implementing a health promotion and physical activity program for people with serious mental illness in community mental health centers. In this study, 48 community mental health centers are randomized to a VLC or to TA. This is, to our knowledge, the first national study to compare the VLC effectiveness with or without ASR, and its methods used and lessons learned to inform

the proposed work. The proposed study addresses a gap in knowledge about the effectiveness of VLC compared to TA, as well as the effectiveness of enhanced data support as part of a VLC.

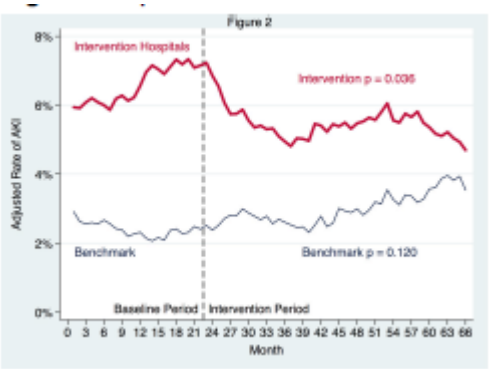
**A.4. Expertise in Automated Surveillance Reporting (ASR).** Our team has expertise in the development and adaptation of statistical surveillance methods,[33,37] risk prediction models in cardiology,[28,38] hierarchical modeling in medical device trials,[39-41] and informatics surveillance and clinical decision support tools[42-45] to conduct retrospective and prospective surveillance of electronic health record and clinical registry derived patient data for the purposes of detecting institutional and provider variation[31,33] and for medical product comparative effectiveness.[45] As part of research funded by NIH, NLM, FDA, and VA, we developed an automated surveillance engine (Data Extraction and Longitudinal Time Analysis [DELTA]) and used for medical device comparative effectiveness trials, and institutional and operator quality surveillance initiatives.[30-33,42]

As an example of prior impact, we used the risk-adjusted sequential probability ratio testing and automated surveillance tools to evaluate a single center cardiac catheterization registry from 2002 to 2006 for operator outliers with respect to all-cause mortality.[33] When compared with national expectations, the institution was found to be within expectations for the outcome, and only one of 18 operators was found to be an outlier. Chart review found that the operator in question experienced a high incidence of compassionate use (salvage procedure or not a surgical candidate). This risk factor was not included in the risk adjustment models, and after excluding all such patient cases, the operator's risk-adjusted mortality rate was within expectation. This resulted in a local policy discussion and informed our work in rolling out a compassionate use variable in the Massachusetts mandatory registry, which improved risk adjustment model performance.[46]

Most relevant to this proposal, we recently improved on the Mehran AKI risk score (c-statistic=0.67)[27] by developing an AKI prediction model in 115,633 diagnostic cardiac catheterization and PCI patients in the VA (c-statistic=0.74) with external validation in 10 non-VA hospitals.[14] We have adapted our surveillance toolkit to survey AKI in the VA health system in a study concluding this year (IIR11292). The surveillance toolkit uses the new VA AKI prediction model and sends tailored automated reports to VA operators on AKI outcomes. We used the newly developed risk model to measure risk-adjusted institutional variation for each of the VA's catheterization laboratories, using the methodology for the ASR tool from our prior work.[31, 32] The risk-adjusted sequential probability ratio test (RA-SPRT) found 8 sites that were worse than expected for AKI event rates and at least 2 sites that were above expectation for 4 years of the 5-year analysis period. In the same period, 7 sites were better than expected for 2 years, and 2 were better than expected for 4 years of the analysis period.

**Aim 2. Supporting Literature.** Besides our publication of the pilot intervention,[1, 3] there is no evidence to document the consistent application of these evidence-based preventive measures for AKI, or evidence to document if an intervention is effective

after the implementation phase. Implementation trials have not evaluated the sustainability of the interventions deployed. It is imperative we test the comparative effectiveness of our interventions and determine if they result in sustainable improvements after they are removed.




**Aim 2. Preliminary Data.** In our pilot intervention (HS018443), we coached and trained teams in methods to implement AKI preventive approaches in their respective centers. During a 32-month intervention period, we observed a sustained improvement in the intervention (**Figure 2**). In Figure 2, adjusted rates of AKI are plotted by month, stratified by intervention (red) and benchmark (blue) hospitals, using interrupted time series analysis. The vertical dashed line marks the start of the pilot intervention.[3] We identified cultural improvements in the awareness of AKI, as well as significant changes in the adoption of standardized IV fluid protocols. However, we did not test whether removing the intervention would sustain a significant reduction in AKI. In our proposed study, we will evaluate AKI reduction 18 months after the interventions are removed and determine whether or not the intervention clusters will demonstrate a sustained reduction in AKI or regress back to a baseline AKI incidence.

**A.5. Significance of the Expected Research Contributions** Impact of proposed study: Our overall objective is to develop successful implementation strategies to prevent avoidable complications of common diagnostic procedures in complex patients such as cardiac catheterization and AKI. We will address how to implement established methods to prevent AKI in patients undergoing cardiac catheterization into routine clinical practice. Through our proposed research, we will directly inform several of the NIDDK priority areas, including 1) *Reducing the incidence of AKI; 2) "Prevention, treatment and management strategies of AKI… with the goal of improving short- and long-term outcomes including morbidity, mortality, progression of CKD, functional independence and quality of life;" 3) "Build upon the emerging opportunities that are the fruits of past research investments."* In addition: 4) This proposal aims to deploy and evaluate the effectiveness of the ASR tools with or without learning collaboratives, which are all open source and can be rapidly deployed in other health care systems to evaluate the more rapid adoption and implementation of evidence-based healthcare for kidney disease; and 5) The successful completion of the study will provide a vehicle for rapid dissemination AKI preventive strategies nationally.

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**B. INNOVATION**

It is estimated that over 70,000 events of AKI could be prevented in the US each year if evidence-based preventive strategies were implemented consistently in usual care for the common diagnostic procedures using contrast dye. Despite compelling evidence and guideline recommendations, few hospitals have consistently applied AKI preventive

measures into routine clinical practice.[1, 47] A new era of clinical trials evaluating the comparative effectiveness of automated surveillance reporting (ASR) with or without learning collaborative targeting the implementation and sustained application of preventive intervention for AKI is warranted. The proposed research is innovative, in our opinion, as follows:

- ✓ First national implementation trial using automated surveillance reporting (ASR) with or without a virtual learning collaborative (VLC) or technical assistance (TA) to improve patient safety endpoints.
- ✓ First national implementation trial testing AKI preventive interventions using ASR, VLC and TA approaches.
- ✓ Provides novel development and evaluation of sustainability and fidelity methods in AKI.

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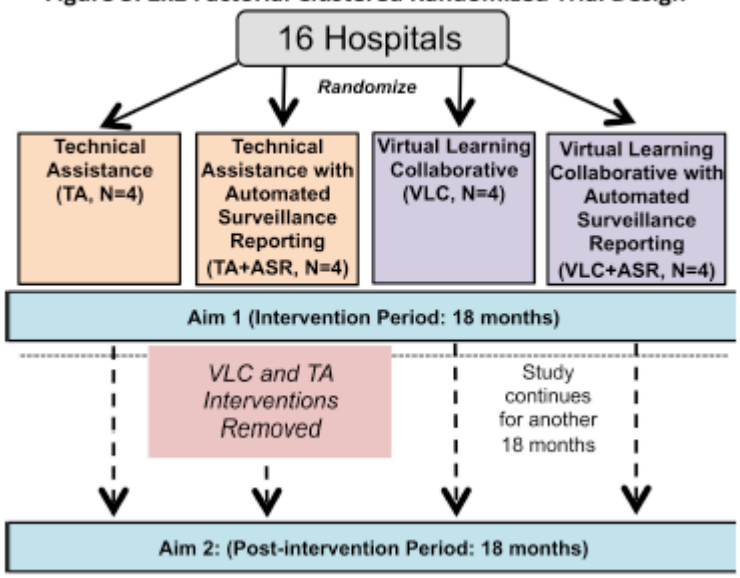
***C. Research Design and Methods:***

**C.1. Specific Aim 1: Compare the efficacy of a Virtual Learning Collaborative and/or Automated Surveillance Reporting compared to Technical Assistance to reduce the incidence of AKI.**

Our *working hypothesis* is that VLC coaching augmented by ASR (VLC+ASR) will be superior to TA, TA + ASR, and VLC alone. Secondarily, VLC will be superior to TA with or without ASR.

Figure 3. 2x2 Factorial Clustered Randomized Trial Design




**C.2. Research Design.** We will conduct a prospective cluster-randomized 2x2 factorial design controlled trial of adult patients undergoing cardiac catheterization with or without intervention within the VA for the primary endpoint of AKI. A 2x2 factorial design is ideal to determine the effect of VLC compared to TA and the effect of ASR compared to no ASR while guarding against confounding by the other factor.[48] This study design also allows for the interaction of the two factors (i.e., the extent to which the effect of one factor varies across the levels of the other) enabling a maximally efficient determination of the optimal intervention strategy. Hospitals will be randomized to receive one of the following interventions: (A) TA; (B) TA+ASR; (C) VLC; (D) VLC+ASR (see **Figure 3**). the target number of patient records that will be reviewed from the EHR will be approximately 10,576 (which is approximately 2,644 in each of the four arms of the study (TA, TA+ASR, VLC, VLC+ASR) with a minimum of four hospitals within each arm (average 661 patients per

hospital)). The intervention phase in all arms will be for 18- months from 7/1/2018 to 12/31/2019. Interventions will stay active during the 18-month post-intervention phase.

In contrast to a one-factor study or an imbalanced two-factor study, a factorial design is advantageous because it allows one to determine firstly whether the factors interact and then simplifying the analysis if there is no interaction to more precisely infer the main effect of each factor all without relying on the validity of an assumed statistical model for the outcomes. We hypothesize that the VLC intervention may have a different effect size depending on whether ASR is used, and this method guards against confounding by the other factor and allows a robust, perhaps more precise, assessment of both factors separately. This study design assumes that each intervention is implemented independently, meaning that the TA and VLC, and ASR and no ASR will all be implemented separately, and the presence of one will not change the intervention of the other.

The proposed trial is guided by the Promoting Action on Research Implementation in Health Services (PARIHS) framework.[49-55] The PARIHS framework and its three dimensions (context, facilitation, and evidence) was selected for addressing these barriers to implementation in AKI prevention.[54]

**C.2.a. Study Population: Site Inclusion and Exclusion Criteria.** All patients at the participating sites will be enrolled into the trial with a series of inclusion and exclusion criteria.

VA Site Inclusion Criteria: All VA medical centers with a cardiac catheterization laboratory are eligible, and all catheterization operators at a site are included.. We currently have over-recruited 29 VA sites, but a minimum of 16 VA sites will be enrolled.

Patient Inclusion Criteria: Among these sites, only patients aged 18 or greater who undergo diagnostic coronary angiography or percutaneous coronary intervention (PCI or angioplasty) will be enrolled in the trial. CKD is of primary interest and it will be determined by a pre-existing CKD diagnosis in the VA medical record, or by two or more estimated glomerular filtration rates <60 (ml/min/1.73 $m^2$) at least 90-days apart prior to presentation. Patient Exclusion Criteria: Patients with a history of dialysis (hemodialysis, peritoneal dialysis) or under the age of 18 will be excluded. Cardiac catheterization (also referred to as coronary angiography) is defined as a procedure in which a catheter is inserted into the femoral or radial artery and is threaded to the cardiac vasculature where radio-contrast dye is administered and a series of x-rays obtained in order to visualize the coronary arterial anatomy. PCI is when a clinical intervention is then performed to address any treatable pathology that is found.

**C.2.b. Randomization.** Randomization will occur at the hospital level in a 2x2 factorial design.[48] We will enroll a minimum of 16 Veteran Affairs (VA) hospitals with cardiac catheterization laboratories from across the United States (see Letters of Support and Facilities) that meet the medical center inclusion/exclusion criteria above. We will use a random number generator and block-randomize centers by the following variables: 1)

VA region (1-4); and 2) patient volume (<800, 800+), see **Table 1** for the sites that initially met out inclusion/exclusion criteria.

**Table 1. VA Site Characteristics**

| Site | Region | Procedure Volume |
|---|---|---|
| 554 | 1 | 1131 |
| 691 | 1 | 807 |
| 605 | 1 | 545 |
| 654 | 1 | 292 |
| 580 | 2 | 1794 |
| 549 | 2 | 1605 |
| 671 | 2 | 1015 |
| 537 | 2 | 629 |
| 586 | 2 | 341 |
| 626 | 3 | 1621 |
| 637 | 3 | 692 |
| 672 | 3 | 632 |
| 544 | 3 | 335 |
| 528* | 4 | 1617 |
| 512 | 4 | 326 |
| 693 | 4 | 266 |
| 632 | 4 | 49 |

*2 sites

**C.2.c. Primary Endpoint.** KDIGO AKI defined by ≥0.30 (mg/dL) or ≥50% increase in serum creatinine over baseline within 48-hours of the procedure or within 7-days for in-patients, or onset of dialysis within 7-days.[13]

**C.2.d. Data Collection and Data Coordinating Center.** We have experience in using existing electronic health record (ViSTa, CPRS) and CART program quality initiative data collection to capture all patient and procedural characteristics, comorbidities, and outcomes in order to identify patients for pre-existing CKD, ascertain AKI outcomes, and to provide the data infrastructure to support the ASR intervention. In order to conduct national risk-adjusted surveillance for participating sites, we will collect data for the first 6 months after study approval at, in each of the 76 VA institutions with cardiac catheterizations laboratories.[14] The CART data is collected through a structured data entry tool in the EHR. As part of a prior research project (VA HSR&D IIR 11-292), we have established a comprehensive automated data center with weekly feeds from CART and daily to weekly feeds from the data domains in the VA Corporate Database Warehouse (CDW), which extract data from the production EHR. For those few data sources with a delay more than a week, we have a supplemental automated tool that uses a VA approved interface layer to extract the data in near-real time from the production EHR. These data are transformed and merged through a validated process into an analytic data cube that can be analyzed to provide reports to operators and hospitals as well as providing data for review. A summary of the currently available data elements from the CART-CL clinical registry and EHR are shown in **Appendix 1**. Individual clinical registry elements conform to the American College of Cardiology National Clinical Data Repository data element definitions.[56] The research team, including the director of CART (CART Letter), has a long history of utilizing these data sources for research.

Due to the 2020 COVID-19 pandemic, many of our enrolled VA site cardiac catheterization laboratories have been temporarily closed or procedures have been greatly reduced. Disruption to normal laboratory procedures could impact the IMPROVE AKI study findings. Therefore, our research team is requesting access the COVID-19 Shared Data Resource in VINCI, containing information relevant to COVID-19 inside and outside the VA.

We will be using the COVID Shared data resource to identify overall rates of testing and COVID positivity at each site that has a cath lab to get a sense of COVID impact at that site. We will also be linking each of the cath patients to COVID testing status to get a sense of how often they were tested, and how many were cath'ed and COVID+. Lastly, we will assess whether COVID+ status had enough patients amonth cath patients to warrant inclusion as a risk factor, since AKI is a risk factor from covid. We will not be

analyzing any case level data from non-cath patients, but will use the COVID shared resource to aggregate as above.

**C.3. AKI Prevention Toolkit.** *Intervention:* All sites will receive the AKI Prevention Toolkit (**Appendix 1**) including 3 core interventions: 1. Standardized order sets; 2. IV and oral fluids; and 3. Reduced contrast volume. The interventions adhere to the KDIGO guidelines[13] and add interventions developed and tested in our pilot intervention to implement AKI preventive strategies.[1,3] We will also educate the sites on the hemodynamic guided fluid administration for volume expansion guidelines and PRESERVE results when released.[57,58]

**C.4. Virtual Learning Collaborative (VLC).** *Intervention:* The VLC will be offered to eight teams (minimum of 4 with ASR, minimum of 4 without ASR) and will receive the AKI Prevention Toolkit.[1,3] Each participating site will be supported to establish a multidisciplinary team charged with continuously improving AKI, which will include interventional cardiologists, cardiac catheterization lab manager and technicians, nursing representatives from the intensive care unit and/or holding areas, cardiology administration, nephrology, and representation from the quality improvement department (VA Clinical Application Coordinator [CAC] and Systems Redesign). Each VLC site team will be assigned 2 expert coaches from White River Junction VA (VA affiliate of Dartmouth): AKI quality improvement specialist and VLC and improvement specialist. A 60-minute VLC training call will be held monthly during the trial. The VLC and VLC+ASR will be coached independently to avoid contamination. All VLC sessions will be conducted using VA Microsoft Teams Meeting and recorded. VLC clusters will have access to shared team materials on VA including, AKI Prevention Toolkit, VLC session recording, uploaded homework from sites (which may include aggregated data on AKI and other factors over time), educational materials, and other tools or documents to support the VLC interventions.

Figure 4. Virtual Learning Collaborative Monthly Calendar

| Week | Activities to be completed |
|---|---|
| 1 | Monthly Report Due to Coach<br>1st of the month (or first workday of the month) |
| 2 | Coaches review team-based reports and send feedback to teams |
| 3 | Monthly Virtual Learning Collaborative session |
| 4 | Coaches available to teams by phone, email, or Adobe Connect as needed |

Each of the sites in the VLC intervention will follow the same structure each month (see **Figure 4**. VLC monthly calendar). On the first of the month, teams will be required to submit homework to "VA VLC O365/ SPO Sharepoint folder," a web-based platform that allows multiple users to access and upload files to be shared among approved members. The monthly homework will ask teams to share about the changes made during the previous month, including a review of successes and challenges. Expert team coaches will review the uploaded homework and provide team-based feedback. There will be a monthly learning lesson call. Each learning session call will consist of several key components: introduction and roll call, review AKI Prevention Toolkit components, process changes or quality improvement methodology, team sharing and/or reports on their work during the previous month. Coaches will be available via phone and email to answer any questions from teams, if requested. See **Table 2** for a description of VLC

and TA call topics, which may be modified based on need. Participation will be measured by activity on the monthly calls, simple progress reports, and participation.

***Table 2. Virtual Learning Collaborative and Technical Assistance Call Topics***

| Month | Clinical Topic | Quality Improvement Implementation Component |
|---|---|---|
| 1 | Getting Started team members/roles Project timeline Overview of bundle interventions from the AK Prevention Toolkit | Components of a learning collaborative Problem identification Model for mprovement Setting Global and Specific Aim Statements |
| 2 | **Intervention 1: Standardize Pre- and Post-Cath Orders** | Planning Process mprovements (Process Maps/Flowcharts) What is the problem? What process will you focus on? What is the current process? |
| 3 | **Intervention 2: IV and Oral Fluid Orders** | Effective Communication |
| 4 | **Intervention 3: Reducing contrast volume** | Causation Fishbone diagrams |
| 5 | ntervention 2 continued NPO status | Change deas Plan Do Study Act (PDSAs) |
| 6 | ntervention 2 continued Patient oral fluids | Measurement Process changes and outcome measures |
| 7 | Review Pre-PC nterventions lessons learned Case 1 2 | Lessons learned from nterventions 1-4 |
| 8 | ntervention 2 continued LVEDP matched hydration | Measures use of playbooks |
| 9 | ntervention 2 continued Delay Cath if V fluid bolus not received | Ladder of inference |
| 10 | Review of Peri-Cath interventions trialed case study lessons learned | Lessons learned from nterventions 5-6 |
| 11 | ntervention 1 Standardize Pre- and Post-Cath Orders - revisit | Accomplishments What is going well or be improved? |
| 12 | ntervention 2 and 3 V and Oral Fluids and Reducing Contrast -revisit | Revisit improvement methods |
| 13 | Review of interventions trialed lessons learned Case 3-5 | Lessons learned from interventions 7-8 |
| 14 | Review of Process Changes mplemented | Planning for sustainability PDSA/SDSA |
| 15 | How to sustain and spread changes in practice | NHS Sustainability Model |
| 16 | Sustainability/Spread NHS Model for Sustainability | NHS Sustainability Model |
| 17 18 | Final Team Reports and Plans for next 18 months post-intervention | Lessons Learned |

*Evaluation and Measurement:* Process measures will be self-reported by participating teams each month in a monthly homework or report identifying the process changes made during the previous month including the bundle interventions implemented during the previous month. Process measure collection will be duplicated by existing field-defined data elements captured by the Data Coordinating Center for which our research team has extensive experience. The report will also ask teams to submit the team meeting agenda and minutes. Process measures are reported in **Table 3**. To supplement these reports, each team champion(s) (current directors of catheterization laboratories) will be tasked with giving a 4-5-minute report on their progress on each VLC call. Based on our pilot, the key process changes to be measured are the use of AKI prevention toolkit, clinical champions, empowered nurses, team

***Table 3. VLC and TA Evaluation and Measures***

| | |
|---|---|
| **Process changes (measured by EMR and collected by sites)** | # bund e nterventons mp emented<br>- Standard zed order sets<br>- IV F u ds<br>- NPO status (reduced to 2 hours)<br>- Pat ent ora hydrat on<br>- Reduced contrast vo ume<br>- LVEDP matched hydrat on<br>- De ay case f IV f u d bo us not rece ved<br># of process changes made, agenda, m nutes |
| **Process measures (measured by EMR and collected by sites)** | 1. NPO durat on (hours)<br>2. Tota ora f u d ast 24 hours (mL)<br>3. IV f u ds ordered pr or to procedure (order vo ume n mL)<br>4. Tota IV f u ds ast 24 hours (mL)<br>5. IV f u d bo us g ven (500+ mL 1-hour pr or to procedure) (yes/no)<br>6. IV at keep ve n open (KVO)?<br>7. IV Pump used?<br>8. Procedure de ayed for IV f u d bo us (yes/no)<br>9. Ca cu ated MACD (5mL x body we ght n kg over base ne serum creat n ne)<br>10. Ca cu ated CrC :Contrast Rat o (3x CrC )<br>11. Left Ventr cu ar End D asto c Pressure<br>12. Contrast vo ume |
| **Outcome** | Acute K dney In ury |
| **Fidelity measures: VLC or TA** | VLC: Adherence to VLC key components:<br>- part c pat on on the month y earn ng ca s (verba , chat box entr es)<br>- subm tted homework or reports<br>- act ve part c pat on n earn ng commun ty<br>- team hudd es outs de of LC<br>TA: Adherence to TA components:<br>- attendance and part c pat on on month y techn ca ass stance ca s<br>- team n t ated contact |
| **Interviews every 6 months** | Improvement tra n ng<br>Improvement efforts<br>Imp ementat on barr ers and successes |

champions, protected time for team meetings, and QI training.[3] A survey will be completed monthly for each team following each call or session through VA RedCap.

**C.5. Technical Assistance (TA).** *Intervention*: TA will be offered to the eight teams randomized to the TA condition (minimum of 4 ASR, minimum of 4 without ASR) and will receive the AKI Prevention Toolkit.[1, 3] TA will have monthly scheduled TA calls (60 minutes each) with each team individually to review and discuss the bundle interventions (as is done in the VLC group) and allow for a consultation with experts on the AKI bundle interventions. TA calls will be driven by an agenda with timely topics used to assess where sites are at with implementing the AKI Prevention Toolkit led by the AKI improvement specialist (Solomon, External Collaborator). All TA calls will be conducted with individual hospitals in each cluster (TA, TA+ASR). The goal of the TA consultation call is to address questions, review progress, and discuss challenges for the sites in implementing the AKI Prevention Toolkit. TA sites are also allowed to raise issues or concerns for discussion. If additional expertise is needed for specific questions, the TA expert will either schedule a follow-up call or respond via email. Teams are allowed to reach out to the TA expert at any point during the 36 months. TA will follow Call Topics in **Table 2**. Fidelity to the TA intervention and semi-structured interviews will be conducted as described in the VLC methods. TA will have the same touch points as VLC. All TA sessions will be conducted using VA Microsoft Teams Meeting and recorded. A survey will be completed monthly for each team following each call or session through VA RedCap.

*Evaluation and Measurement:* The process changes and primary outcomes (AKI) will be the same as those teams in the VLC (see **Table 3**. VLC and TA Evaluation and Measures). Fidelity measures for TA will include individual attendance at the 4 scheduled calls and team initiated contacts (see Appendix 1). Semi-structured phone-based interviews will also be conducted every 6 months for 18 months with TA team members to learn about improvement training, efforts, and implementation barriers and successes (see VLC methods).

**C.6. Automated Surveillance Reporting (ASR).** *Intervention:* ASR will be offered to eight teams (4 with VLS, 4 with TA) as noted above in block randomization.[1,3] The surveillance tools will execute a weekly updated estimation of each site's risk-adjusted performance, which generates a set of data that will populate series of tables and graphs for each site. There will be 3 levels of granularity (**Figure 5A**): 1) National Risk-Adjusted Ranking (**Figure 5B**) that reports the overall performance of each site relative to the national expectation, 2) Site Specific Performance Summary (**Figure 5C**) which highlights whether the site is out of expectation with regards to the statistical process control based methods used for sequential surveillance, and 3) patient list, which provides a table of the patients, with columns for each of the risk factors in the risk adjustment model and the predicted risk for the outcome and observed outcome (**Figure 5D)**.

The figures and graphs will be placed inside a PDF directly along with text describing the methods used in the analysis, and an attached excel sheet of the 3rd level patient list report, which includes demographics, risk variables used in risk adjustment, the predicted risk of the outcome, and the observed outcome value for each patient at that site. The same data and format will be populated within a website with an identical workflow (**Figure 5**) and visualization to the PDF that users can log in and review the current and historical data of their site and all other catheterization sites within the VA intranet at any time. Only those sites randomized to receiving ASR (n=8) will be able to access the dashboard or receive the PDF's vial email link. This type of internally 'public' reporting has been shown in prior literature to potentially be more impactful than de-identified reporting, and we have the CART approval to operationalize the ASR reporting.

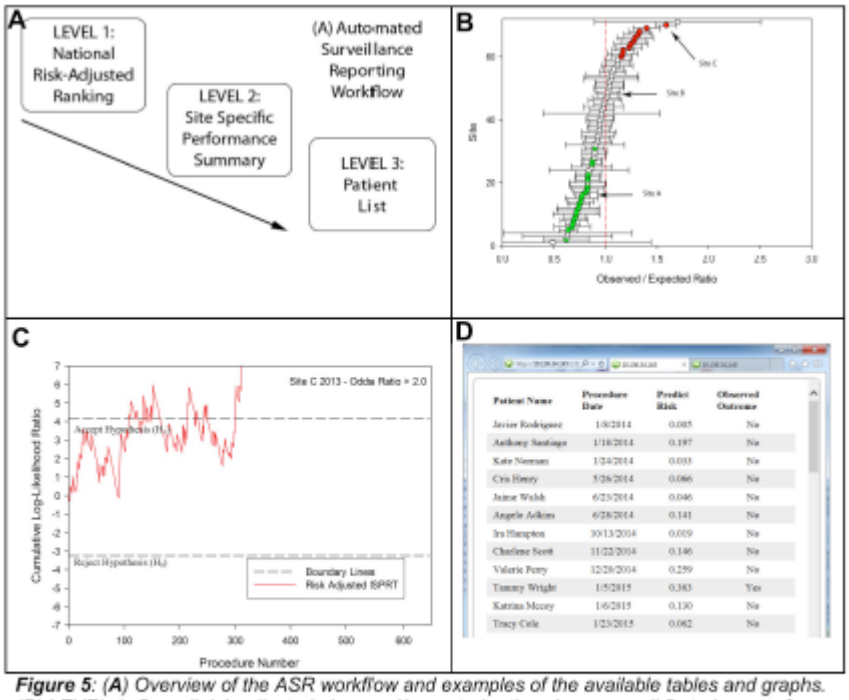



***Figure 5**: (**A**) Overview of the ASR workflow and examples of the available tables and graphs. (**B**) LEVEL 1: Overall risk-adjusted observed/expected ratio values over all 5 study years for each VA cardiac catheterization center. (**C**) LEVEL 2: RA-SPRT surveillance for Site C, which is noted to be above risk expectation, for alpha and beta errors of 0.10 and an odds ratio of 2.0 risk adjusted as noted previously. (**D**) LEVEL 3: Dashboard view of synthetic patient list for Site C that includes overview data as well as values for risk variables used in risk adjustment (additional variables not shown).*

Within either the web or excel-embedded-in-PDF user interface, users will be able to review patient data from their site to see which patients experienced the AKI outcome and to explore the analytic data for which factors were most likely related to AKI. This allows users maximal flexibility to inform their site-specific quality improvement initiative. Lastly, should a deeper chart review be desired, patient identifiers are available in the Level 2 Patient List portion of the tool to allow a user to open the EHR to conduct a deeper review and/or conduct other activities as part of their QI initiative protocols. Within the analytics module, the risk prediction models for post-procedural AKI will be developed monthly using the risk-adjusted sequential probability ratio test analysis method testing an odds ratio of 2.0 with a type I error of 0.05 and a type II error of 0.10, and a retrospective rolling 1 year window prior to the current month using the LASSO variable selection method applied to all candidate variables included in our previously published national risk model development work.[59] LASSO is conservative in its variable selection; unlike Ridge regression which merely shrinks coefficients LASSO pushes coefficients of weaker predictors to 0. The rolling window allows for continuous risk model recalibration, which is considered best practice for the use of risk prediction models due to calibration drift over time. For each model, discrimination (measured by the AUC) and calibration (by Cox intercept and slope) will be calculated and reported.[60, 61]

*Evaluation and Measurement:* As noted above, the primary endpoint of AKI following cardiac catheterization will be assessed within the 2x2 study design. A number of process measures will be assessed as secondary endpoints, in a similar pattern to those reported for the VLC intervention. A survey will be administered monthly to each team with access to the ASR through VA RedCap as required progress reports prior to each monthly session (**Appendix 4**): whether they felt the information provided by risk-adjusted performance ratings was useful, whether access to the patient reviewer dashboard tool was helpful, and whether it influenced the implementation process during that month. Other characteristics will be captured through website logging and PDF report download usage statistics, which is tied to user authentication/direct download URL and will allow tracking of how often users and sites access the information and which parts of the report are viewed and utilized. We will analyze whether the use of the ASR increases or decreases over the course of the study and whether the use is different between the TA and VLC sites that have access to the ASR. To ensure that we capture the key process changes, team champions will submit responses to the mandatory monthly questionnaire for ASR (**Appendix 4**). A survey will be completed monthly for each team following each call or session through VA RedCap.

**C.7. Statistical Analysis.** We will conduct a 2x2 factorial analysis using a two-level hierarchical model that adjusts for observed patient covariates included in our VA AKI pre-procedural risk model and accounts for the clustering of patients within hospitals in comparing the effects of the four interventions comprising VLC, TA, and ASR on AKI.[14] Adjusting for patient case-mix accounts for differences in the distribution of patient covariates across intervention groups, thereby removing chance confounding in the sample (randomization implies that the expected confounding is 0), and yields more

precise estimates by accounting for the effects of patient-level factors that would otherwise inflate the error variance. Because ASR is a binary variable, we use a hierarchical logistic regression model with a two-way ANOVA at the hospital-level as the base model for estimating the effects of the interventions on patient outcomes. Let $AKIij$, $VLCi$, $ASRij$, and $Patientij$ denote the value of AKI, the hospital's VLC status (1 = VLC, 0 = TA), the hospital's ASR status (1 = Used, 0 = Not used), and a vector of observed covariates for the *j*th patient in hospital *i*. The model for this analysis is specified as follows: logit(Pr ($AKI_{ij}$ = 1|$\theta i$)) = $\beta_0$ + $\beta_1$ $VLCi$ + $\beta_2 ASRi$ + $\beta_3 VLCi$ $ASRi$ + $\beta_4^{\mathrm{T}} Patient$ + $\theta i$ + $\varepsilon_{ij}$ (1) where $\theta_i \sim Normal(0, \tau^2)$ and $\varepsilon_{ij} \sim Normal(0, \sigma^2)$. Under (1), the regression parameters $\beta_1$ through $\beta_4$ denote the effects of VLC (versus TA) in the absence of ASR, the effect of ASR in the absence of VLC (i.e., under TA), the difference in the effect of VLC when ASR is present compared to when it is absent, the patient covariates, respectively, while $\tau^2$ is the unexplained between-hospital variation, and $\sigma^2$ is the unexplained between patients within hospital variation. We will first examine the significance of the interaction effect, $\beta_3$. If this is significant we will report separate effects for VLC (versus TA) for when ASR is present than when it is absent – the effects obtained under a 4-level one-way ANOVA design (one level for each intervention strategy) – to enable the optimal intervention strategy to be easily seen. If an interaction is not present we will drop $VLC_i$ $ASR_i$ from the model in (1) and estimate the resulting no-interaction two-factor model to obtain more precise estimates of the main effects of VLC and ASR and of the optimal treatment strategy.[48] Under both scenarios, multiple comparisons will be accounted for using Bonferroni correction methods and we will limit regression adjustment to the pre-specified set of patient predictors described in the next section to guard against selectively choosing the model that yields the most favorable result. An alternative to using regression adjustment to account for patient characteristics in (1) is to use propensity score methods to balance the treatment groups with respect to patient case-mix – with only a minimum of 16 sites being randomized it is not unreasonable to anticipate some differences in the distribution of patient characteristics between the 4 groups, despite our blocking the sites. Because propensity score matching across 4 groups will be cumbersome, we will use inverse probability weighting by the propensity scores. However, the a priori expected propensity score for the four groups is 0.25 and using weights inflates standard errors and lowers power, propensity score weighting will only be performed as a sensitivity analysis. In addition, we will evaluate the trial against non-intervention control groups using both a historical non-intervention control group among the enrolled sites in this trial and a concurrent non-intervention control group from a sample of non-enrolled sites in the national VA. Additional analyses on AKI from retrospective national catheterization procedures to support and inform the AKI interventions may be conducted including AKI prediction, trends overtime, trends and use of preventive practices (for example, IV fluid volume use, contrast volume use, etc).

**Cost-effectiveness evaluation.** We will assess both the clinical effectiveness in AKI reduction and the two interventions' cost-effectiveness. A cost effectiveness analysis will be conducted estimating the incremental cost for each incremental AKI prevented above the TA only baseline and stratified across the other three clusters. A

separate budget impact analysis for implementing the VLC arm and stratified by ASR will be generated. Budget impact analyses estimate the cost to the hospital or service entity to implementing a new program or initiative.

**C.8. Qualitative Methods.** We will employ a qualitative approach in assessing site **fidelity** to the randomized intervention arm (TA, TA+ASR, VLC, VLC+ASR) and **implementation** of the interventions. Building off prior quantitative and qualitative work conducted by our research team, we will measure fidelity to the VLC, including participation on monthly calls, submission of key documents (i.e., homework), and a general active participation in the learning community in months 12 to 18 (see **Appendix 2**). We have mapped data collection tools including fidelity and implementation measures to the PARIHS framework constructs (see **Appendix 3**) to ensure we gather appropriate information for the context, facilitation, and evidence domains in PARIHS.[54] Semi-structured phone-based interviews with all team members together (without the catheterization laboratory director) at each site (TA and VLC) will occur at baseline, month 12 and 18 post-intervention to collect qualitative data on the participant experiences with the improvement process (**Appendix 3**). With these interviews, we hope to examine aspects of clinic culture that may support or hinder AKI prevention and the dynamics and organizational culture of the clinic. Such information (e.g., hierarchies and power dynamics, consensus and disagreement) will augment our understanding of barriers and facilitators of AKI prevention within real-world clinical settings.[62,63] Interviews will be conducted at each site for each team member. These 1-hour interviews will be conducted using an interview guide to solicit in-depth information about the work of the staff, including the strategies to prevent AKI. Two qualitative researchers will lead the qualitative approach in assessing fidelity and implementation. Building on our prior work,[3] interviews will ask about the fidelity of the appropriate strategies identified in our pilot work to improve AKI. We will also inquire about barriers and facilitators of implementing the identified strategies. Interviews, TA and VLC calls will be audio-recorded using a VA-approved audio recorder (VA Microsoft Teams Meeting) and transcribed by an approved federal contractor, Transperfect, and used for qualitative analysis (**C.8. Qualitative Analysis)**.

**Qualitative Analysis.** Audio-recorded qualitative interviews will be transcribed, managed and analyzed with the aid of Atlas.ti, a qualitative analytic software program. We will conduct qualitative content analysis, a widely-recognized strategy for the interpretation of the content of text through systematic coding to identify patterns and themes.[64] We will approach our analysis through four coding levels: 1) descriptions of a priori themes based on the interview guide, 2) fidelity of the interventions, 3) unanticipated or emergent themes, and 4) barriers and facilitators to the implementation of strategies to improve AKI. Qualitative coding and content analysis will consist of identifying quotations that express a cogent theme or concept and labeling these quotations for categorization and summarization.[65] Coding is the pivotal link between data collection and deriving meaning from qualitative data.[66,67] In the initial stages of coding, we will conduct 'open' coding, which is the process of labeling portions of text to identify and formulate all ideas, themes, and issues suggested by the data.[66,68] Analytic

codes constructed in the context of open coding are provisional and grounded strongly in the data.[66,69] Through ongoing immersion in the dataset, we will proceed to 'focused coding', which utilizes the prominent themes identified during open coding as the basis for more fine-grained analyses.[69] We will compare different pieces of data for similarities and differences, known as a *constant comparisons* approach (comparing different pieces of data for similarities and differences). This will be done until no new categories or relevant themes emerge (point at which *thematic saturation is* reached).[70]

Two analysts will code the qualitative data. Involving multiple analysts is a highly-regarded check on rigor in qualitative research as it allows for multiple perspectives and resolution of discrepancies through consensus.[69] We will review our coding approach and conduct regular consultations with the research team during the coding process. Based on previous qualitative studies, the selected sample size for the interviews is anticipated to achieve saturation of themes. Our analyses will yield an in-depth understanding of efforts and strategies to improve AKI at VA Medical Centers. We expect our findings will be generalizable to all VA and non-VA medical centers and generate hypotheses relevant to future efforts designed to improve AKI.

**C.9. Scientific Rigor and Sex as a Biological Variable**. We will enroll all eligible consecutive patients in our study including women. Our model includes the patient characteristics of sex and age. This will allow us to assess the beta coefficients of these biological variables and plot their marginal effects on AKI outcomes and their influence on our findings. While women are a smaller proportion of patients in the VA, sex will be incorporated (1 = woman, 0 = men) to determine mediating effects in women versus men and age will be modeled as a spline function to assess curvilinear effects dependent on patient age.

**C.10. Rigor and Reproducibility.** To ensure scientific rigor and reproducibility, an analytic program file used to produce the analyses and a de-identified dataset will be made available to third parties within the VA system to conduct confirmatory analyses for the proposed specific aims. All parties must be in compliance with VA regulations and access. All analytic results will be reported in supplementary appendices for all publications.

**C.11. Sample Size and Power.** To be conservative, power calculations assume the two-factor ANOVA with interaction. The target enrollment of approximately 2,644 is planned in each of the four arms of the study (TA, TA+ASR, VLC, VLC+ASR) with four hospitals within each arm (average approximately 661 patients per hospital). Based on national VA catheterization data for CKD patients,[14] the proportion of AKI in the VLC and VLC+ASR arms are assumed to be 0.2700 under the null hypothesis and 0.2025 under the alternative hypothesis (an effect size of 25% or 0.0675). The proportion of AKI in TA and TA+ASR arms are projected at 0.2700 for the intervention period. We further assume an intra-cluster correlation coefficient (the ratio of variation between hospitals to the sum of variation within and between hospitals) of 0.0009 – this is implied by the intervention arm of the pilot study.[3] We plan to conduct 0.05-level tests and desire

power of at least 90%. The power for analysis to detect any difference at all across the four intervention studies can be approximated by assuming the distribution of the proportion of AKI cases under each strategy follows a normal distribution and applying an F-test with penalty for clustering. Under these assumptions, our power to detect any difference against the null of no difference is above 99%. We also compute power for illustrative individual contrasts of interest. The power to detect a significant effect of VLC within a level of ASR (i.e., either for ASR used or ASR not used) is also above 99% (although numerically lower than for the test of any difference across the four groups as sample size is halved) with a minimum detectable effect size of 0.034. If under the alternative hypothesis the proportion of AKI for the VLC arm was also 0.27 (so that an interaction effect is present), the power to detect a significant interaction between TA/VLC and ASR status is just above 90%. Power is lower for the interaction contrast due to four groups being compared as opposed to only two groups. In summary, we have overwhelming power to detect a difference among any of the four intervention strategies and between the levels of one factor within a level of the other factor, and acceptable power (i.e., above 90%) to detect a significant interaction between the effects of the factors. Finally, assuming a Bonferroni correction for multiple testing and a 25% effect size for each difference, testing the full set of 6 pairwise differences among the four intervention strategies has power >97% implying we will be adequately powered to infer the optimal intervention strategy.

**C.12. Expected Outcomes.** We expect to prevent AKI and improve outcomes in common diagnostic procedures. As depicted by the above power calculations, we expect to reject the null hypothesis that the interventions (TA, TA+ASR, VLC, VLC+ASR) will all produce the same reduced rate of AKI after the 18-month intervention period. Comparable to our pilot intervention, we expect the VLC with or without ASR to have more than a 25% reduction in AKI over the TA intervention with or without ASR, where we observed a 28% reduction among patients with pre-existing CKD,[3] implying that the above power calculation likely errs on the side of being too conservative (i.e., we expect to have greater power). Using process measures from our fidelity tool and interviews, we expect to observe the VLC teams to successfully implement more AKI prevention strategies from our toolkit. At our 6-month semi-structured interviews of individual team members, we expect team members to report their teams achieving a hospital-wide shift in the attitudes and awareness of AKI prevention comparable to our pilot.[3]

**C.13. Generalizability to non-VA sites.** The VA offers a strong learning laboratory with existing standardization across sites. The VLC intervention was piloted in 10 non-VA hospitals. The ASR intervention, while developed in the VA for national ASR for AKI, can be ported to any EMR; daily data from the EMR laboratory or catheterization system would need to be directed to the mounted ASR toolkit in the data warehouse. Coding to allow the ease of portability to non-VA EMRs will be conducted by Dr. Matheny's Core during the award period. The AKI Prevention Toolkit and measures can be applied in any VA or non-VA site.

**C.14. Potential Problems and Alternative Strategies.** One potential problem is **site enrollment**. Sample size estimates required a minimum of 16 sites (minimum of 4 in each arm); we have over-recruited 29 sites with planned over-enrollment in each arm to a minimum of 4 sites per arm; the two excess sites with the lowest volume will be excluded from the study. Another potential threat is **contamination** where providers from one condition educate providers in the comparison condition of their implementation group. Indeed, this is the reason why we have chosen to randomize at the site as opposed to the physician level, for which contamination would be highly plausible. In regards to our proposed site-level cluster design, we control for potential contamination by constraining team communications to the 4 sites in the same study condition. In addition, only the ASR sites will have website access to the ASR resources regulated by user login requirements. In addition, while login access is restricted to ASR, it is possible that ASR centers could directly share surveillance data with a non-ASR site, but beyond basic site risk-adjusted ranking, all other data will focus only on that site, which will limit possible contamination. First, we will evaluate the possibility of contamination through both quantitative measures of process improvements and qualitative data from calls and semi-structured interviews of team members. Second, we have systems in place to prevent transfer of recommendations on AKI Prevention Toolkit implementation from VLC sites or summary statistics on relative performance from the ASR sites to the TA site(s) or non-ASR site(s). Third, the TA sites will have the same number or calls, TA sites will not have access to the VLC structure, frequency, or level of team-based coaching. We have taken care in both the design and measurement to ensure contamination does not occur and if it does, it will inform our analysis.

Site level randomization may generate patient level imbalances between sites, and this requires that we adjust for patient-level characteristics in the statistical analyses as noted above (see Statistical Analysis).

Ascertainment of AKI is a potential issue for measurement bias. By focusing on patients with pre-existing CKD, we will limit the number of patients currently without measurement of serum creatinine up to 48- hours. Based on our extensive experience with the CART data and supplementary serum creatinine data from multiple sources within the VA, less than 5% of patients with pre-existing CKD do not have a post-procedure serum creatinine measured within 48-hours. Current VA standard of care is to have post-procedure serum creatinine measured for all CKD patients. We will strongly encourage sites to implement a routine clinical practice that is in compliance with the current guidelines as part of our educational quality improvement framework.

While setting up the study, we will be able to collect data from sites for a period of approximately 6-months before any interventions are unleashed. One strategy is to use these data to establish baseline covariates for each site, helping to account for unexplained variation between sites. However, with the ICC estimated to only be 0.0009, there is likely to be little utility in this. Another use is to allow the 4 intervention strategies to be compared to a pure control or baseline in which no intervention is used by pooling these data with the data.

**C.15. Specific Aim 2: Evaluate the sustained efficacy of the Virtual Learning Collaborative and/or Automated Surveillance Reporting to reduce the incidence of AKI following the intervention period.**
Our *working hypothesis* is that teams coached in the Virtual Learning Collaborative with and without Automated Surveillance Reporting will sustain reductions in AKI following the intervention period. All 16 hospitals will continue to monitor patients following the 18-month intervention period for an additional 18-month post-intervention period. We will evaluate whether or not the reduced incidence of AKI will be sustained following the removal of the TA, VLC, and ASR interventions. Although this aim is focused on the period 19-36 months post-intervention, randomization holds for the purpose of comparing the effect of the interventions on differences in patient outcomes (particularly AKI) during this period. In the event Aim 1 yields a null finding, Aim 2 will still be valuable if (1) the onset of the intervention effect might only manifest after month 18, or (2) the effect is constant, or nearly constant, in which case analyzing the pool of observations over the entire 36-month period may yield a significant finding even if the 1-18 month analysis does not.

**C.16. Research Design**. After 18-months, the TA, ASR, and VLC interventions (Aim 1) will all be removed, and all hospitals will be followed for an additional 18-months with continued data collection and semi-structured interviews (Aim 2). Following the Aim 1 trial, we will conduct a prospective cohort with AKI as the primary endpoint. All sites will be followed for an additional 18-months with data collection and interviews; hospitals will be blinded to the follow-up and interviews conducted at the end of the post-intervention 18-month period. The target number of patient records that will be reviewed from the EHR will be approximately 10,576 (which is approximately 2,644 in each of the four arms of the study (TA, TA+ASR, VLC, VLC+ASR) with four hospitals within each arm (average 661 patients per hospital)). During the 18-month post-intervention period, we will compare the sustained efficacy of the interventions using formal 2x2 factorial design and longitudinal interrupted time series analysis. All interventions will be actively continued in the post-intervention phase (months 19-36).

**C.16.a. Study Population: Inclusion and Exclusion Criteria.** The study sample of interest for each of the analyses in Aim 2 will include all adult patients undergoing cardiac catheterization within the Veteran's Health Administration from among hospitals randomized in Aim 1. The same inclusion and exclusion criteria from Aim 1 will be applied. The Aim 2 post-intervention enrollment period will occur from January 1, 2020, to June 30, 2021, for a period of 18-months.

**C.16.b. Primary Endpoint.** KDIGO AKI defined by ≥0.30 (mg/dL) or ≥50% increase in serum creatinine over baseline within 48-hours of the procedure or within 7-days for in-patients, or onset of dialysis within 7-days.[13] We also constructed a **Sustainability Measure**: sites will demonstrate sustained implementation if all 3 core interventions are reported to be in place from **Table 2** (1. Standardized order sets; 2. IV and Oral Fluids; and 3. Efforts to reduced contrast volume). We will ask each site to report on the

sustained implementation of the 3 core interventions. In addition, assessment of the process changes will be determined by routine patient data collection, site audits, and be informed by the National Health System Institute for Innovation and Improvement Sustainability Model.[71] This model will guide teams in planning to sustain efforts by measuring the effectiveness of the program and adaptability of the improved process, focusing on process, staff and organizational factors influencing sustainability. Measures include 10 factors to assess the sustainability of the program (**Table 4**).[71] Factor Level number is selected for each factor to describe the sustainability of the intervention and summed to a score ≤100 (≥55 is positive; ≤45 indicates concern).

**Table 4. NHS Factors Influencing Sustainability**

| NHS Sustainability Model Sections | NHS Sustainability: Individual Factors |
|---|---|
| Process | Benef ts beyond he p ng pat ents<br>Cred b ty of Ev dence<br>Adaptab ty<br>Mon tor ng progress |
| Staff | Tra n ng and nvo vement<br>Att tudes<br>Sen or Leaders<br>C n ca eaders |
| Organ zat on | Infrastructure<br>F t w th Goa s and Cu ture |

**C.16.c. Data Collection and Data Coordinating Center.** The data coordinating center will collect all data elements from each hospital during the post-intervention 18-month period as reported in Aims 1. In addition to evaluating the primary population with pre existing CKD, we will also evaluate all cardiac catheterization patients. Data collection will include all cardiac catheterization procedures from 2000 through 2024 to support analyses and models for AKI. Patients and procedures will exceed 510,000, in addition to the CKD patients in the clustered randomized trial (~10,576 [C.16]).

**C.17. Statistical Analysis.** We will compare the rate of AKI during the 18-month post-intervention period (i.e., the period 19-36 months out from the initiation of the interventions) between the interventions using an identical approach to Aim 1 including **scientific rigor and biological variables** analysis.[48] The reason why the approach is identical is that the only change is that a different cohort of patients will be analyzed. Although the interventions will have ceased, the study design is unaltered. Therefore, the model in (1) will be estimated and if appropriate simplified using the same procedure and will be followed by re-evaluation of the same hypotheses. Following the primary analyses, we will explore the longitudinal relationship between the intervention and post-intervention periods. The analysis will be performed by pooling the data from the intervention (1-18) and post-intervention (19-36) month periods. In the base specification, we will define a variable $Postij$ (= 1 for the post period and 0 for the intervention period) and add interaction variables between $Postij$ and each of $VLCi$, $ASRi$, and $VLCiASRi$, to the model in (1). (The main effect of $Postij$ will be added to the model only if time is not otherwise represented in the model.) If the effect of the interventions wanes over time, we expect that the $Postij$ interaction effects will reduce the overall magnitude of the intervention effects. More generally, we will explore the time-sequence of the interventions to determine if there were statistically significant shifts or trends in rates of AKI over time.[72] We will explore whether the effect of the

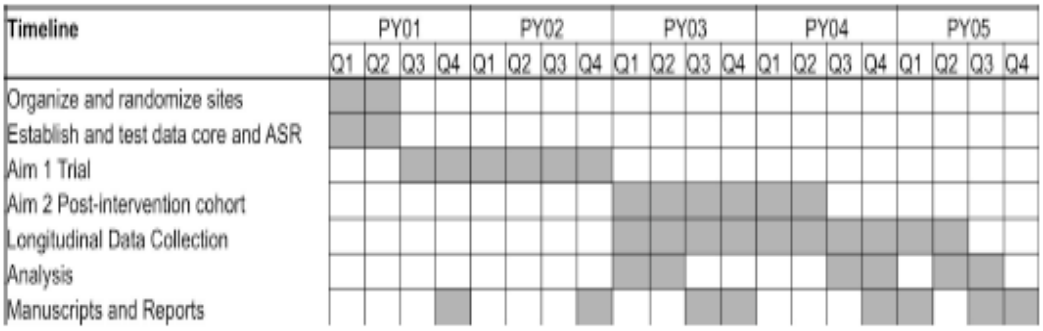
interventions changes with time both within the intervention period and then with respect to time after the intervention period ends.

**C.18. Sample Size and Power.** Since we expect to enroll the same number of patients during the 18-month period after the active interventions cease as, in the 18-month period of the active intervention, the power to detect the same effect sizes as considered for Aim 1 remains unchanged. The test for an interruption in the effect 19-months from the start of the intervention is an exploratory analysis and so we do not compute power.

**C.19. Expected Outcomes.** We expect to sustain a lower incidence of AKI and improve outcomes. Using process measures, we expect to observe the VLC teams during the post-intervention period to successfully sustain the implementation of more AKI prevention strategies from our toolkit. Using 6-month semi-structured interviews of individual team members, we expect team members to report that their team and hospitals are achieving a hospital-wide shift in the attitudes and awareness of AKI prevention comparable to our pilot.[3] We expect the VLC to be sustainable using our measure of Sustainability.

**C.20. Potential Problems & Alternative Strategies.** Unlike Aim 1, we will not be concerned with contamination in Aim 2 after all interventions are removed. However, comparably to our approach in Aim 1, we will still evaluate the possibility of contamination of the intervention arms, ensure complete ascertainment of AKI, and address the potential of patient imbalance in randomized clusters in our multilevel modeling approach described in the statistical methods (**C.7**). We will measure the possibility of contamination through quantitative measures of process improvements and qualitative data from calls and interviews with team members. Should Aim 1 not demonstrate significant differences between the 4 intervention arms, Aim 2 will continue to monitor the endpoints and conduct a trial autopsy from the robust quantitative and qualitative data including site audits to determine fidelity to the interventions, and ability of sites to implement improvements.

**C.21. Timeline.** The study will be carried out over five years. VA site recruitment has already been completed (Letters and Facilities attached). Since our interventions and data coordinating center have been established from other federally-funded projects, we will be able to initiate the interventions by project year 01, month 7. The cluster-randomized trial period will run from PY01 through the



end of PY02. Post-intervention will run from PY03 to PY04. Longitudinal data, analyses, and reports will be completed in PY05.

**C.22. Future Directions.** Our *overall objective* of this project is to increase the consistency with which AKI preventive approaches are applied. We expect the consistent application of our interventions will have a *positive impact* on reducing morbidity and mortality following cardiac catheterization in the 16 VA sites randomized in our study. The successful evaluation of our implementation interventions will determine which intervention or combination of interventions (e.g., VLC+ASR) could be used as a vehicle for rapid dissemination or AKI preventive strategies across the VA and other non-VA hospitals. We have established inexpensive and adaptable implementation interventions to disseminate guidelines and evidence-based practice to multiple hospitals and teams for the prevention of AKI. In our opinion, these strategies could also be used to rapidly disseminate new landmark trial findings, such as PRESERVE, as well as the implementation of new technologies to prevent AKI in the cardiac catheterization population. In the future, our implementation interventions could be adapted to coach teams in managing and preventing CKD, CKD progression, and ESRD. Our implementation interventions could also be adapted to work with dialysis unit teams in VLC methodology to assist in overcoming barriers and challenges in maintaining ideal hemoglobin, sodium, and potassium levels used as quality indicators for patient safety and dialysis unit performance. This study will address an important gap in the literature to reduce the high variability in complications of common procedures for complex patients and how the VLC+ASR model could be applied in other populations to reduce avoidable morbidity, mortality, and healthcare costs.

**C. 23. Specific Aim 3: Laboratory Predictors of AKI in Patients Undergoing Coronary Angiography**

Prior studies using the Veterans Health Administration coronary angiography cohort have developed robust, externally validated prediction models for AKI; however, it is still unclear if certain less well-studied laboratory markers in this context are risk factors for AKI. Hypomagnesemia, for example, is associated with a higher risk of AKI in patients receiving cisplatin, as well as in non-cancer patients. In a cohort of ~20,000 cardiac surgery patients, we found that hypomagnesemia (defined as a serum magnesium level <1.5 mg/dl) is associated with a 1.8-fold higher odds of the composite outcome of severe AKI, need for renal replacement therapy (RRT), or death, even after multivariable adjustment. We also found that lower pre-procedure hemoglobin and higher hemoglobin A1c are each independently associated with a higher risk of AKI after cardiac surgery.

Study Design: In this specific aim, we will examine whether lower serum magnesium, lower hemoglobin, higher hemoglobin A1c, and other laboratory predictors are associated with a higher risk of AKI in patients undergoing coronary angiography. We will also examine whether laboratory predictors are associated with an increased risk of

death at 30 days. The exposures will vary based on the individual analyses; however, the inclusion and exclusion criteria will be the same:

Data Collection: The cohort of interest will be all patients undergoing cardiac catherization in the VA, per the parent data collection above.

Inclusion criteria: VA adult patients who underwent coronary angiography during the last 10 years (2008 to 2018)

Exclusion criteria:
-End-stage renal disease (ESRD) on dialysis
-Missing baseline SCr
- No post-procedure SCr available within 7 days
-Missing a pre-procedure value of the laboratory predictor of interest (e.g., magnesium, HbA1c, hemoglobin)
-AKI at the time of coronary angio, defined as a ≥2-fold increase in SCr from baseline value to most proximal value prior to coronary angio or any RRT within 7 days prior

Primary Endpoints: Major Adverse Kidney Event within 7 days (MAKE7_1 or MAKE7_2), defined as ≥1.5-fold or ≥2-fold increase in SCr within 7 days, need for RRT within 7 days, or death within 7 days. We are defining AKI as a doubling of serum creatinine (SCr) or need for RRT.

Statistical Analysis: We will conduct a multivariate anlaysis for the outcome of the primary endpoints as noted above, adjusted for the covariates already described in the prior aims, names patient demographics, laboratory tests, medication administrations, and numerous clinical conditions defined as combinations of administrative codes.

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***D. Performance Sites:***

- The Dartmouth Institute for Health Policy & Clinical Practice, Epidemiology, Biomedical Data Science at the Geisel School of Medicine at Dartmouth College– *Coordinating site* (Affiliate of White River Junction VA)
- Vanderbilt University, Department of Biomedical Informatics, Vanderbilt University Medical Center (Affiliate of TVHS VA)
- Tennessee Valley Healthcare Systems, Department of Veteran Affairs
- University of Vermont, University of Vermont Medical Center

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***E. Study Population:***

**E.1. *Patients***

**E.1.a. Inclusion Criteria for VA Patients**

The following conditions must be met for study eligibility:

1) Adults are defined as those patients aged 18 or greater
2) All patients presenting for diagnostic coronary angiography or percutaneous coronary intervention (PCI or angioplasty) to one of the enrolled VA hospitals will be enrolled in the trial. CKD is of primary interest and it will be determined by a

pre-existing CKD diagnosis in the VA medical record, or by two or more estimated glomerular filtration rates <60 (ml/min/1.73 $m^2$) at least 90-days apart prior to presentation.

**E.1.b. Exclusion Criteria for VA Patients**

Patients meeting any of the following criteria will not be eligible to participate in the study:

1) Patients with a history of dialysis including hemodialysis, or peritoneal dialysis.

**E.2. *Implementation Site Staff***

All staff members participating in team-based interventions will be interviewed at baseline, 12, and 18 months following the Virtual Learning Collaborative and Technical Assistance interventions. We estimate to interview 5 to 10 staff members at each of the 16 sites participating in the study. The staff members will include the cardiac catheterization laboratory director, nurse managers, cardiologists, nephrologists, and technicians.

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***F. Research Specific Risks:***

In this project, we proposed to compare the effectiveness of clinical team-based interventions implementing continuous improvements in routine care. Specifically, we will test four interventions: a virtual learning collaborative with automated surveillance reporting (VLC+ASR); a virtual learning collaborative without automated surveillance reporting (VLC); technical assistance with automated surveillance reporting (TA+ASR); and technical assistance without automated surveillance reporting (TA). Experienced AKI and implementation science coaches from White River Junction VA (VA affiliate of Dartmouth) will provide the team-based coaching intervention. Sites receiving VLC interventions will participate in monthly VLC calls together. Sites receiving TA will receive coaching on an individual basis. Sites receiving automated surveillance reporting (ASR) will receive bi-weekly reports tailored to each individual operator in the cardiac catheterization laboratory at that site. Human subjects will include patients and hospital staff members. Patients will provide consent to undergo the cardiac catheterization or percutaneous coronary intervention as routine care at the site of care. All data collection will be derived from routine care within the VA and remain within the VA health system. Teams will continuously work to improve routine care to prevent AKI at their respective sites. Since teams are participating in interventions to improve routine care, patients will not need to consent to participation in the study. Data collection and analysis will remain within the VA and be de-identified for analysis and automated surveillance reports. Clinical team members (staff) will undergo interviews throughout the study period including the cardiac catheterization laboratory director, nurse managers, cardiologists, nephrologists, and technicians. While we will not collect written consent from staff participants, we will inform the staff that interviewers will not collect their names, roles, or institution or report this information in a published report of the project outcomes. F.1.2. The primary risk to all human subjects (patients or staff) is the potential risk to confidentiality.

The risks involved in the participation in this study are very minimal and are outweighed by the potential benefits. There is no physical testing or additional laboratory testing involved beyond routine care. Only standard clinical practice will be implemented with improvements to that practice. No research interventions or tests will be conducted, only team-based interventions and automated reports to operators for the continuous improvement of routine care. Patients without a post-procedural laboratory completed for serum creatinine at the time of discharge will be sent home with laboratory orders (slips) for completion at 48 hours. Post-procedure laboratory measurement of serum creatinine is routine safe and effective care for patients with pre-existing CKD as the development of AKI is associated with a higher risk of short- and long-term mortality and renal failure.

**F.1 Recruitment and Informed Consent**

**F.1.1. Recruitment Strategy**

All VA Medical Centers have been recruited for the study and agreed to randomization. All patients meeting eligibility criteria will be enrolled in the study. Therefore, patient recruitment will not be performed at each site. Data on all cardiac catheterization patients will be pulled to the data core. Patient eligibility will be determined both at each VA site and by the data core. Each site will ensure data fields are populated and follow-up serum creatinine is measured. The data core will determine eligibility and populate analytic datasets for both bi-weekly automated surveillance reports and for the final statistical analysis of the study.

Implementation site staff for team and individual organizational change evaluations will be selected by the Organizational Change Evaluators. (WRJ VA-Dartmouth Team). The cardiac catheterization laboratory director has agreed to randomization and site participation in the project. VA staff will be invited to participate via email prior to participation in the semi-structured interview. Staff participation is completely voluntary, and at any point, they can withdraw from the study. They will not be coerced or influenced to participate, and they will not face any consequences for withdrawal from the study. All staff completing interviews and questionnaires throughout the study will be required to provide verbal consent by the WRJ interviewer prior to initiating the interview. To prevent coercion and address undue influence, all semi-structured interviews will be handled by the WRJ VA-Dartmouth Team.

**F.1.2. Consent Procedures**

The clinical staff will test the implementation of evidence-based preventive interventions through a Virtual Learning Collaborative (VLC) with and without the novel use Automated Surveillance Reporting (ASR) intervention to change clinical practice and improve patient safety in common diagnostic procedures. VA Medical Center cardiac catheterization laboratory directors will provide informed consent to verify agreement to the specified inclusion criteria and to randomization as an implementation site. VA clinical staff participants at the randomly chosen implementation sites will be

approached by WRJ VA-Dartmouth-trained interviewers and provided verbal informed consent to participate in the semi-structured interviews. Invited VA staff work with a multidisciplinary team at each site, which includes the cardiac catheterization laboratory director, nurse managers, cardiologists, nephrologists and technicians. Staff will provide verbal informed consent at the time of the evaluation to answer questions from interviewers (see semi-structured interview sheet in grant appendix). Interviews will be conducted without the catheterization director present. Transcriptions from the interviews will not be provided back to the VA site and retained by the Dartmouth investigative team for coding and qualitative analysis for 1 year following the end of the stud. VA patients will not need to provide consent to receive IMPROVE-AKI interventions continuously improving routine care taking place at the site where they are undergoing cardiac catheterization or PCI. Data collection is automated through the data core and will remain within the VA health system. Implementation site staff participating in organizational change evaluations will provide verbal informed consent at the time of the evaluation and interviews on the Virtual Learning Collaborative. The other staff required for the organizational change evaluations will provide verbal informed consent given that their participation in the interviews is essential to evaluate the IMPROVE-AKI implementation and organizational change. Prior to the organizational change evaluations, there will be an explanation in staff verbal consents explaining to all staff that their position (e.g., Hospital Administrator, Clinician, Allied Health Professional) rather than their name will be recorded on notes of their interviews and that neither their names nor the name of their hospital will ever be used in any published report of the study.

That being said, hospitals participating in the Virtual Learning Collaborative will be informed that their progress in implementing the IMPROVE-AKI program will be shared with other members of their Virtual Learning Collaborative, consistent with the practices of running Collaboratives. Staff will also be informed that both the organizational change assessments and the Virtual Learning Collaboratives will be audiotaped solely for the purpose of qualitative review and consensus ratings. These audiotapes will be maintained until they can be transcribed, with titles/positions substituted for any names on the tapes.

**F.2. *Protection Against Risks***

The risks associated with sites, staff, and patients participating in this study are very minimal and are outweighed by the many potential benefits of improved patient safety and outcomes. There is, however, a slight risk in the loss of confidentiality.

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**G. *Confidentiality and privacy for the subjects*:**

**G.1.1. Protection Against Breach of Confidentiality of VA Patients**

The risk regarding the breach of confidentiality of VA patient participants will be controlled by retaining all data within the VA health system. Data collection will be automated within the VA health system to the data core operated by Dr. Michael Matheny. Dr. Matheny is the Associate Director of the VA Informatics and Computing

Infrastructure (VINCI) and has developed a near-real-time data core pulling data from all the VA cardiac catheterization laboratories and VA data from the VA Corporate Data Warehouse (CDW). This established infrastructure will be leveraged to maintain the highest standards of data security and maintain confidentiality for our VA patients at all times. Data managers will be thoroughly trained in data safety. All data is securely held on locked stationary encrypted servers and password protected. All demographic information is coded by catheterization procedure ID numbers. Subject confidentiality will be carefully maintained. Patient identifiers will be stored in the master file; however, patient and provider identifiers will be stripped from the analysis database. The analysis database will be held to the same security standards and maintenance and will be used to conduct the statistical analysis all being retained within the VA health system. All data collectors, managers, and analysts will undergo human subjects' protection and data information security training prior to working on the study. Subject's identities will not be discussed, presented or published within this study.

**G.1.2. Protection Against Breach of Confidentiality of VA Staff**

Risk regarding breach of confidentiality of VA staff interview data from organizational assessments will be minimized by recording staff position (e.g., Hospital Administrator, Clinician, Allied Health Professional) rather than their name, which will be recorded on notes of their interviews and that neither their names nor the name of their hospital will ever be used in any published report of the study. The same methods will be done when audiotapes are transcribed. We will never use staff names or site names in any published report of the study. Instead, we will code the sites with consecutive numbers from 1-12. That being said, sites participating in the Virtual Learning Collaborative will be informed that their progress in implementing the IMPROVE-AKI program will be shared with other members of their Virtual Learning Collaborative, consistent with the practices of running these types of collaboratives.

**G.1.3.**

**G.1.3.I. Informed Consent**

A. All VA Medical Centers have been recruited for the study and agreed to randomization. The cardiac catheterization laboratory director has agreed to randomization and participation in the project. VA staff will be invited to participate via email prior to participating in the semi-structured interview. Staff participation is completely voluntary, and at any point, they can withdraw from the study. They will not be coerced or influenced to participate, and they will not face any consequences for withdrawal from the study. All staff completing interviews and questionnaires throughout the study will be required to provide verbal informed consent to participate before the interview begins. To prevent coercion and address undue influence, all semi-structured interviews will be handled by the WRJ VA-Dartmouth Team.
B. The data for all patients meeting eligibility will be collected and included in the analysis of the primary and secondary endpoints.

**G.1.3.II. Data Safety, Quality, and Management**

A. No patient contact will occur in this study. The patient data obtained from Electronic Health Records (EHRs) will only be used. Data for this study will be collected prospectively through the VA electronic medical record. Routine data feeds from the VA electronic medical record, CART (NCDR catheterization procedure data, laboratory values, AKI, and outcomes including AE and SAEs will populate the database at the data core under the supervision of Dr. Michael Matheny. All data elements from the NCDR cardiac catheterization national database, which is sent to CART in Denver, CO, will be sent to the data core. All patient laboratory results will be sent to the data core. Automated surveillance reports will only include de-identified data and in aggregate form. The target enrollment of approximately 2,644 is planned in each of the four arms of the study (TA, TA+ASR, VLC, VLC+ASR) with four hospitals within each arm (average 661 patients per hospital). Based on national VA catheterization data for CKD patients, the proportion of AKI in the VLC and VLC+ASR arms are assumed to be 0.2700 under the null hypothesis and 0.2025 under the alternative hypothesis (an effect size of 25% or 0.0675). The proportion of AKI in TA and TA+ASR arms are projected at 0.2700 for the intervention period. We further assume an intra-cluster correlation coefficient (the ratio of variation between hospitals to the sum of variation within and between hospitals) of 0.0009 – this is implied by the intervention arm of the pilot study. We plan to conduct 0.05-level tests and desire power of at least 90%. Once the study is complete, a de-identified dataset will be created for the final unblinded statistical analysis. The analysis will be conducted within the VA and not transported outside the VA to ensure data security. Although we do not foresee any risk or adverse events, blinded and unblended datasets will be created semi-annual review. All data will be reviewed for protocol adherence, including a data verification check that the appropriate outcome measures are given at the appropriate time points. Interim and final reports will be given to VA central IRB, as well as the study sponsors. In addition to evaluating the primary population with preexisting CKD, we will also evaluate all cardiac catheterization patients. Data collection will include all cardiac catheterization procedures from years 2000 through 2024 to support analyses and models for AKI totaling more than 510,000 patients and procedures.
B. All data is securely held on locked stationary encrypted servers and password protected. All demographic information is coded by catheterization procedure ID numbers. Subject confidentiality will be carefully maintained. Patient identifiers will be stored with the master file; however, patient and provider identifiers will be stripped from the analysis database. The analysis database will be held with the same security standards and maintenance and will be used to conduct the statistical analysis all being retained within the VA health system.
C. Blinded and unblended data reports will be developed.
D. The Data and Safety Monitoring Plan (DSMP) will adhere to the protocol approved by NIH. A Data and Safety Monitoring Board (DSMB) charter will be created and members will be appointed to provide additional oversight of the trial. The DSMB will meet and review data bi-annually throughout the project. The DSMB will include experts in the

following scientific disciplines with expertise in cardiology, nephrology, and statistics to interpret the data and ensure patient safety. The DSMB will not include the PIs or members from the VA. The DSMB will review the protocol and data collected to date, and advise the Co-PIs on any potential risks as well as on any risk mitigation plans.

**G.1.3.III. Confidentiality**

A. Confidentiality will be maintained during all phases of the study, including monitoring, preparation of interim results, review, and response to monitoring recommendations.
B. Retaining all data within the VA health system will control confidentiality of VA patient participants. Data collection will be automated within the VA health system to the data core operated by Dr. Michael Matheny. Dr. Matheny has developed a near-real-time data core pulling data from all the VA cardiac catheterization laboratories. This established infrastructure will provide the highest standards of data security and maintain confidentiality for VA patient participants.
**C.** Recording staff position rather than their name will control confidentiality of VA staff. Neither VA staff names nor name of their hospital will be used in any published report of the study

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***H. Benefits:***

VA Medical Centers who are randomly assigned to the Virtual Learning Collaborative may benefit substantially from the opportunity to receive high-intensity team coaching to implement the AKI preventive strategies and learn from other teams participating in the Virtual Learning Collaborative as they continuously work through the process of implementing the AKI preventive strategies. The support provided by the coaches and other teams participating in the Virtual Learning Collaborative may enable the sites to create sustainable protocols and cultural changes to prevent the occurrence of AKI in patients undergoing cardiac catheterization or PCI at the site once the interventions are removed. Likewise, sites who are randomly assigned to the Technical Assistance intervention will receive intermittent team-based coaching and tools to prevent AKI at their site, which may enable the site to create sustainable protocols and cultural changes to prevent the occurrence of AKI in patients undergoing cardiac catheterization or PCI at the site once the Technical Assistance is removed. For sites randomly assigned to receive automated surveillance reporting, individual operators and teams may benefit from biweekly customized reports that may assist the teams in monitoring and identifying actionable improvement opportunities. The automated surveillance reporting will likely assist sites in creating the sustainable protocols and cultural changes to prevent the occurrence of AKI. Patients will benefit from high-quality care, which will likely improve routine care as the study progresses. The teams we have created to address the issue of AKI will provide the best evidence based medical care known for preventing and treating AKI following PCI. Patients may independently benefit from this on-going work and will benefit future patients. The benefit to risk ratio is very high, given the extremely low level of risk involved in participation.

This study has the potential to substantially add to the evidence base and scientific knowledge on the sustainable adoption of AKI preventive strategies delivered through inexpensive team-based coaching programs and simple automated reports to catheterization laboratory operators. The successful implementation of the AKI preventive strategies will reduce the incidence of AKI and likely prevent progression of CKD, ESRD, and mortality as demonstrated in our previous research. Given the number of preventive strategies for AKI, it is essential to learn how to engage teams and hospitals to implement and sustain those preventive strategies in order to prevent AKI and other long-term consequences of AKI. While our study will focus on the implementation of AKI preventive strategies, the results of our study could be applied to the implementation of other patient-safety interventions in cardiac catheterization laboratories. By collecting implementation data, we will better understand how to successfully disseminate AKI preventive strategies to hospitals across the United States and the world.

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***Cost and Compensation:*** There will not be any costs or compensation to subjects.

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***Medical Record Review:***

Data for this study will be collected prospectively through the VA electronic medical record. Routine data feeds will populate the database at the data core under the supervision of Dr. Michael Matheny. All data elements from the NCDR cardiac catheterization national database, which is sent to CART in Denver, CO, will be sent to the data core. All patient laboratory results (in- and out-patient) will be sent to the data core. Automated surveillance reports will only include de-identified data and in aggregate form. Once the trial is complete, a de-identified dataset will be created for statistical analysis. The analysis will be conducted within the VA and not transported outside the VA to ensure data security.

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