An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial

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ABSTRACT

Background Variable standards of care may contribute to poor outcomes associated with AKI. We evaluated whether a multifaceted intervention (AKI e-alerts, an AKI care bundle, and an education program) would improve delivery of care and patient outcomes at an organizational level.

Methods A multicenter, pragmatic, stepped-wedge cluster randomized trial was performed in five UK hospitals, involving patients with AKI aged ≥18 years. The intervention was introduced sequentially across fixed three-month periods according to a randomly determined schedule until all hospitals were exposed. The primary outcome was 30-day mortality, with pre-specified secondary endpoints and a nested evaluation of care process delivery. The nature of the intervention precluded blinding, but data collection and analysis were independent of project delivery teams.

Results We studied 24,059 AKI episodes, finding an overall 30-day mortality of 24.5%, with no difference between control and intervention periods. Hospital length of stay was reduced with the intervention (decreases of 0.7, 1.1, and 1.3 days at the 0.5, 0.6, and 0.7 quantiles, respectively). AKI incidence increased and was mirrored by an increase in the proportion of patients with a coded diagnosis of AKI. Our assessment of process measures in 1048 patients showed improvements in several metrics including AKI recognition, medication optimization, and fluid assessment.

Conclusions A complex, hospital-wide intervention to reduce harm associated with AKI did not reduce 30-day AKI mortality but did result in reductions in hospital length of stay, accompanied by improvements in in quality of care. An increase in AKI incidence likely reflected improved recognition.


AKI is common, and it is associated with markedly elevated short-term morbidity and mortality, subsequent risk of CKD, and large increases in health care resource utilization.1 AKI occurs in 5%–22% of hospital admissions, and mortality rates exceed 20%, rising to >50% in those most severely affected.2 In the absence of specific therapies, AKI management requires methodical delivery of basic elements of care.3 Despite universal recommendation of this approach in national and international guidelines,4–6 successive reports have described variation in the quality of clinical care for AKI, with poor standards of care associated with worse outcomes.7–10 Although there are no proven interventions for AKI, the evidence base to support organizational-level interventions to address

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variations in AKI care is also lacking. In the only previous randomized trial, a text message alert for AKI did not change physician behavior or patient outcomes, possibly because the alert was introduced without recommendations for care or other interventions.11 Conversely, several nonrandomized studies testing broader interventions, generally using before-after comparisons, have shown more positive results, including reductions in mortality, although methodological concerns prevent firm conclusions from being made.12–15 Additionally, all but one of these studies are single center, and therefore, they do not inform on whether successful interventions retain effectiveness if scaled to other organizations. We, therefore, sought to address some of these knowledge gaps by performing a multicenter, randomized trial to test the hypothesis that a complex intervention for AKI (comprising AKI e-alerts, an AKI care bundle, and a program of AKI education) would improve standards of care delivery and lead to better patient outcomes.

**METHODS**

**Study Design and Participants**

Over a 27-month period, we conducted a multicenter, pragmatic, stepped wedge cluster randomized trial (SWCRT). The study was conducted using a published protocol,16 which was consistent with the extension to cluster randomized trials of the Consolidated Standards Of Reporting Trials 2010 document17 and recommendations for SWCRTs.18 The protocol and statistical analysis plan were published on the National Health Service (NHS) England Think Kidneys Program website19 and are included in Supplemental Material.

The SWCRT design allowed for differentiation between the effect of the intervention and independent time-related factors while avoiding ethical concerns around withholding treatment in line with minimum care standards, with all sites exposed to the intervention by study end. Cluster randomization avoided contamination of the control group that would likely occur with randomization at a patient level.

The intervention, designed to reduce avoidable harm associated with AKI, was introduced across five NHS hospital sites representing academic and nonacademic centers as well as those with and without onsite nephrology services. Data collection and analysis were conducted independently by researchers not involved in the delivery of the intervention at the participating hospitals.

The SWCRT design involved delivery of the intervention sequentially to one hospital at a time across fixed 3-month periods until all five hospitals were exposed to the intervention (Figure 1). A 6-month baseline period before any of the sites introduced the intervention was followed by five 3-month implementation steps (one hospital per step). The 3-month time period during which a site introduced the intervention, when it was expected not to have reached full effect, was considered a transition period and excluded from analyses. All sites had a minimum of one 3-month period of exposure to the intervention after the transition period.

We included all patients ages ≥18 years old who were hospitalized for at least one night during the study period and sustained AKI during that admission. Patients were defined as having AKI if they had an inpatient serum creatinine result consistent with a modified Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI as identified by the NHS England algorithm. A full description of the algorithm has been published previously,20 but in brief, the algorithm applies the KDIGO criteria to an individual’s current serum creatinine value using a baseline value defined as either the lowest in the last 7 days or a median of values from the preceding 8 to 365 days depending on availability of previous results. Urine output was not used to define AKI for pragmatic reasons. The only exclusion criterion was chronic dialysis for ESRD. The Derbyshire Research Ethics Committee designated the study as service improvement and waived the requirement for individual patient consent. Transfer and collation of patient data by the United Kingdom Renal Registry (UKRR) were approved by the Health Research Authority under section 251 of the NHS Act 2006.

**Randomization and Blinding**

The unit of randomization (the cluster) was the participating hospital. Randomization was performed by the UKRR and took place on the 11th of May 2015 using random number generation (SAS-9.3, RANUNI function). The first hospital commenced implementation in June 2015. There were no delays to the SWCRT sequence. Because of the nature of the intervention, blinding was not possible.

**Intervention**

The intervention had three components designed to improve AKI recognition and the delivery of basic elements of AKI care as recommended by National Institute for Health and Care Excellence Clinical Guideline CG169 and other national and...
Perform urinalysis
Review medications and stop those contributing to AKI
Treat sepsis
Assess volume status and optimize BP

Table 1. Core elements that were included in care bundles at each of the Tacking AKI study sites

<table>
<thead>
<tr>
<th>Centre 1</th>
<th>Centre 2</th>
<th>Centre 3</th>
<th>Centre 4</th>
<th>Centre 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline data collection (pre-intervention)</td>
<td>Intervention (transition period)</td>
<td>Intervention (transition period)</td>
<td>Intervention (transition period)</td>
<td>Intervention (transition period)</td>
</tr>
</tbody>
</table>

Figure 1. Schematic of the stepped wedge study design. After a 6-month period of baseline data collection, the intervention (hospital-wide AKI e-alert, care bundle, and education program) was sequentially introduced to participating sites across fixed 3-month periods of time until all sites were exposed to the intervention. Data collection occurred at each step of the wedge, including in the post-intervention period. The 3-month time period during which a site introduced the intervention, when it was expected not to have reached full effect on outcomes, was considered a transition period and excluded from analyses. All sites had a minimum of one 1-month period of exposure to the intervention after the transition period. The sequence was determined by random number generation, and the order of the hospitals was as follows: (1) Frimley, (2) Bradford, (3) Ashford and St. Peters, (4) Leeds General Infirmary, and (5) Leeds St. James.

Table 1. Core elements of the AKI Care Bundle Common across All Sites

<table>
<thead>
<tr>
<th>Core Elements of the AKI Care Bundle Common across All Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess volume status and optimize BP</td>
</tr>
<tr>
<td>Treat sepsis</td>
</tr>
<tr>
<td>Review medications and stop those contributing to AKI</td>
</tr>
<tr>
<td>Perform urinalysis</td>
</tr>
<tr>
<td>Referral (to nephrology or critical care outreach) for AKI stage 3, AKI with complications</td>
</tr>
</tbody>
</table>

Sites were permitted to tailor the appearance of care bundles, and some sites included additional elements (e.g., additional investigations into cause of AKI, management of hyperkalemia, and informing patients of the presence of AKI).

setup phase ensured that the algorithm was running correctly in each laboratory. The detection algorithm ran at all sites throughout the study period, with alerts being released to clinicians at the point when the hospital was randomized to introduce the intervention. The alert message notified the health care professionals that the patient had sustained AKI and the stage of AKI, and it included an advice message advising a clinical response/review of the patient and sign posting of local AKI resources (guidelines and care bundles). All sites also adopted an active element to the alert in that the duty biochemist would telephone AKI stage 2 and 3 results to the clinical areas from which the blood tests were sent (as opposed to a purely “passive” alert within the results reporting system that relies on clinicians seeing the result autonomously).

The care bundles at each site all contained the same core elements (Table 1), although initial care bundle content and design were refined in response to end user feedback during the first 3 months of use. This led to a degree of variation in the number of actionable items in the care bundles between hospitals. Care bundles were delivered in paper form, and they were integrated into patients’ hospital notes apart from one center, where the care bundle was in electronic form.

Education was mainly delivered by face to face teaching across a number of different settings, but also, it included the development of educational materials, e-learning, and awareness raising. Formal teaching sessions were typically delivered using PowerPoint presentations, whereas ad hoc or opportunistic teaching on wards was focused around real time patient examples or sign posting project resources. A summary of educational activities that were delivered in each hospital is shown in Table 2.
The intervention was delivered by an AKI project team at each hospital, which consisted of staff provided by the central team (project managers M.J., N.J., and C.J.), principle investigators (J.S., Y.S., A.J.L., R.R., and N.S.), and hospital staff not funded by the project.

Outcomes

The primary outcome was 30-day mortality after an episode of AKI comparing control and intervention periods. Predefined secondary outcomes included incidence of hospital-acquired AKI, AKI progression to higher stages, incidence of individual AKI stages, and length of hospital stay (LoS).20 We defined hospital-acquired AKI as that with its onset ≥24 hours after hospital admission, and AKI progression was defined as an increase of one or more AKI stages from time of detection.23 After LoS analysis, a post hoc analysis was undertaken for duration of AKI (calculated as days between first and last serum creatinine results that met the definition of AKI). Technical issues prevented data collection for two prespecified secondary end points (number of critical care bed days and renal recovery).

Outcome data were collected using biochemical results to identify episodes of AKI, which were then linked to data from each hospital’s patient administration system to determine patient identifiers and demographics, dates of admission and discharge, all diagnosis codes from the index admission (as per the International Classification of Diseases, Tenth Revision [ICD-10] and the Charlson comorbidity score),24 and date of death. These data were transferred directly to the UKRR from each site independent of the study teams, and they were analyzed by an independent statistician. NHS tracing was performed by the UKRR at the end of the study to identify any additional out of hospital deaths. Summary data for each hospital were generated for each 3-month period for total number of adult admissions grouped by age, sex, and ethnicity to allow for calculation of AKI incidence. In September 2016, there was an computer systems failure of the laboratory information management system (LIMS) that served three of the participating hospitals. This meant that the AKI detection algorithm was not available, and laboratory data collection was not possible during this period. For this reason, the trial was extended to allow for an extra period of data collection (December 2016 to February 2017) so that the planned number of data collection blocks was achieved; data from the affected period were excluded.

Process outcomes included the proportion of patients receiving elements of basic care (AKI recognition, fluid assessment, medication review, investigation, senior clinician/specialty review, and care bundle usage) as determined by repeated cycles of clinical audit (30 sequential patients per site from each 3-month data collection period, giving a planned sample of 1050 patient notes evenly distributed across AKI stages 1–3). A standard data collection form and a data specification sheet were used; these are included as Supplemental Material.

Sample Size Calculation

An a priori sample size calculation was undertaken.25 The total number of annual hospital admissions across the five sites

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Table 2. Description of educational program activities that were delivered across sites

<table>
<thead>
<tr>
<th>Type of Education Session</th>
<th>No. of Sessions per Center</th>
<th>Target Audience</th>
<th>Audience Size</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Launch event</td>
<td>1</td>
<td>All members of staff welcome; hospital chief executive, medical director, chief nurse attended</td>
<td>30–50</td>
<td>1 h</td>
</tr>
<tr>
<td>Hospital grand rounds</td>
<td>2</td>
<td>All grades of physicians, doctors in training and open to those in other specialties who wish to attend</td>
<td>40–80</td>
<td>1 h</td>
</tr>
<tr>
<td>Departmental educational or clinical governance meetings</td>
<td>3–8</td>
<td>Departmental teaching to a range of specialties (e.g., emergency medicine, acute medicine, surgery, urology, rheumatology, elderly care)</td>
<td>10–20</td>
<td>1 h</td>
</tr>
<tr>
<td>Postgraduate teaching for doctors in training*</td>
<td>3/yr (1 for each grade of doctor)</td>
<td>AKI teaching as part of curriculum (essential teaching) for doctors in training, attendance often mandatory</td>
<td>20–40</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Induction teaching for new staff*</td>
<td>1–3</td>
<td>Shorter sessions, more focused on process rather than education per se</td>
<td>20–40</td>
<td>15 min</td>
</tr>
<tr>
<td>Nursing, pharmacy, and advanced practitioner teaching</td>
<td>2–3</td>
<td>Varied between centers from small group teaching to formal AKI study day for large groups</td>
<td>5–70</td>
<td>1 h to whole day</td>
</tr>
<tr>
<td>Ward-based teaching sessions</td>
<td>5–10</td>
<td>Formal teaching sessions at ward level</td>
<td>1–10</td>
<td>5–30 min</td>
</tr>
<tr>
<td>Ad hoc teaching sessions</td>
<td>20+</td>
<td>Informal teaching delivered by various members of the AKI team, included reminders of resources, patient-based teaching</td>
<td>1–3</td>
<td>Varied, usually only minutes</td>
</tr>
</tbody>
</table>

Other activities included publicity activities and e-learning/ use of online teaching videos.

*Activities that were already in place before the study.
(434,000) was taken from the Health and Social Care Information Centre (www.hscic.gov.uk; April 2014 to March 2015). The most conservative published rates for assumptions of the proportions of hospital admissions with AKI (2.5%)\textsuperscript{26} and 30-day mortality (16%)\textsuperscript{27} were used. Power was set at 80%, \( \alpha \) was set at 0.05, and a range of values for intracluster correlation between 0.01 and 0.2 was considered. With a trial study time of 2 years, five participating sites (one per randomization step), one transition period per site, and the design effect of the SWCRT\textsuperscript{25} we calculated that, to detect an absolute decrease in 30-day mortality of 3.2%,\textsuperscript{12,13} 10,850 AKI episodes should be studied.

Statistical Analyses
Analysis of 30-day mortality was undertaken using multilevel logistic regression at the individual patient level, with hospital modeled as a random effect and adjusting for time, patients’ covariables (age, sex, and comorbid conditions), and the effect of seasonality. We pooled time into quarterly intervals treated as equally spaced in analytic models. Only first hospitalizations in those patients with multiple AKI episodes were included; results were similar when analyses used last or multiple episodes per patient. The primary outcome response was the estimated mortality odds ratio for the intervention versus the control period.

Secondary analyses were also undertaken at the individual patient level, again adjusting for time, patients’ covariables (age, sex, and comorbid conditions), cluster (hospital), and the effect of seasonality. AKI incidence was calculated using the total number of overnight hospitalization episodes within each time period as the denominator and analyzed using multilevel negative binomial regression. AKI progression was analyzed as a binary outcome for each overnight hospitalization episode using multilevel logistic regression as for the primary outcome (excluding AKI stage 3). The hospital LoS and AKI duration data were highly skewed, and the fit of prespecified Poisson and negative binomial regression models was poor (inadequate correlation between observed versus predicted values). Therefore, quantile regression models were fitted to allow for comparisons at points across the whole distribution (after adjustment for age, sex, comorbid conditions, time, season, and center) in addition to comparison of average values; this approach does not make assumptions about the distribution of the dataset and is robust against the presence of gross outliers.\textsuperscript{28,29} For LoS analyses, only patients who survived to hospital discharge were included. Statistical analyses were conducted at the UKRR in collaboration with the University of Bristol using Stata MP12 and SAS 9.3.

RESULTS
During the study period, there were a total of 316,413 hospital admissions from which a total of 24,059 AKI episodes occurred in 20,179 patients, giving a crude incidence of 7.6 AKI episodes per 100 admissions. During the control period, there were 14,042 episodes (58.4%), with 10,017 (41.6%) in the intervention period. The distribution across AKI stages was as follows: 62% of episodes were AKI stage 1, 21% were stage 2, and 17% were stage 3; 12,507 episodes (52%) were hospital acquired. Patient demographics in control and intervention periods are shown in Table 3, and data for individual hospitals are shown in Supplemental Table 1. Differences in the populations served by each site and the SWCRT design (meaning that sites contributed different amounts of data to control and exposed periods depending on their place in the randomization sequence) resulted in differences in patient demographics between control and intervention periods. These differences between control and intervention periods were not seen when comparing patient demographics at a hospital level. We also observed a significant effect of season on AKI incidence, with higher AKI rates observed during winter (rate ratio in winter [December to February], 1.08; 95% confidence interval [95% CI], 1.02 to 1.13; \( P<0.01 \) compared with spring [March to May]). Outcome analyses were adjusted for these covariables.

The 30-Day Mortality
Crude 30-day mortality across the entire study period was 24.5%; 30-day mortality was not affected by the intervention. In the fully adjusted model (Table 4), the odds ratio for 30-day mortality in the intervention period versus the control period was 1.04 (95% CI, 0.91 to 1.21; \( P=0.55 \)). Analyses performed for individual AKI stages and for community- and hospital-acquired AKI separately also did not show any difference in 30-day mortality between intervention and control periods.

AKI Incidence
After adjustment for other variables, the incidence of AKI was higher in the intervention period compared with the control period (incidence rate ratio, 1.12; 95% CI, 1.03 to 1.22; \( P<0.01 \)). The same effect size was observed across each stage of AKI when analyzing separately (Supplemental Table 2). The increase in AKI incidence was mirrored by a large increase in the proportion of patients with a coded diagnosis of AKI (ICD-10 code N17.X) during the intervention period (adjusted incidence rate ratio, 1.27; 95% CI, 1.15 to 1.39; \( P<0.001 \)), suggesting improved AKI recognition.

LoS and AKI Duration
A total of 18,887 admissions in which the patient was discharged alive were included in the LoS quantile regression analyses. The median hospital LoS for all AKI admissions was 9 days (interquartile range, 4–19). LoS was reduced in the intervention period as shown in Figure 2. The effect was seen in those with longer LoS (from quantiles 0.5 upward). At the 0.5 quantile, the effect size was a reduced LoS of \(-0.7 \) days (95% CI, \(-1.3 \) to \(-0.2 \); \( P=0.04 \)), extending to \(-1.3 \) days (95% CI, \(-2.5 \) to \(-0.2 \); \( P=0.03 \)) at the 0.7 quantile. When the analysis was repeated to include all admissions, regardless of...
whether the patient was alive at discharge, the same pattern of results was observed (Supplemental Figure 1).

Similarly, we observed a reduction in AKI duration during the intervention period; these data are shown in Figure 3. The median duration of AKI was 2 days (interquartile range, 1–4). The effect of the intervention was seen in those at the 0.7, 0.8, and 0.9 quantiles; at the 0.8 quantile, the reduction in duration of AKI was −0.7 days (95% CI, −1.2 to −0.2; P = 0.01).

Quartile regression was chosen in place of the prespecified analyses for LoS and AKI duration, because both negative binomial and Poisson regression showed a significant lack of model fit with poor residual plots. However, results from these analyses were consistent with those from quartile regression. With negative binomial regression, LoS was decreased in the intervention period by 6.6% (95% CI, 1.3% to 11.6%; P = 0.02). With Poisson regression, LoS was decreased by 6.2% (95% CI, 4.7% to 7.7%; P < 0.001). With negative binomial regression, AKI duration decreased by 14.7% (95% CI, 8.8% to 20.3%; P < 0.001), and with Poisson regression, AKI duration decreased by 14.0% (95% CI, 11.4% to 16.5%; P < 0.001).

**Table 3. Patient demographics in control and intervention periods**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of AKI episodes</td>
<td>14,042</td>
<td>10,017</td>
</tr>
<tr>
<td>Men, %</td>
<td>50.3</td>
<td>48.1</td>
</tr>
<tr>
<td>Age group, yr, %</td>
<td>75.4</td>
<td>76.6</td>
</tr>
<tr>
<td>Charlson comorbidity score, %</td>
<td>15.7</td>
<td>15.3</td>
</tr>
<tr>
<td>Individual comorbidities, %</td>
<td>27.2</td>
<td>29.8</td>
</tr>
<tr>
<td>Social deprivation score, a %</td>
<td>34.3</td>
<td>40.8</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td>86.1</td>
<td>85.3</td>
</tr>
<tr>
<td>Social deprivation score, a %</td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Peak AKI stage, % per stage</td>
<td>3.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Hospital-acquired AKI, b %</td>
<td>53.8</td>
<td>49.4</td>
</tr>
</tbody>
</table>

Unadjusted data are shown, and differences between control and intervention populations largely reflect the different amounts of data submitted to control and intervention periods as a result of the stepped wedge cluster randomized trial design. There were no major differences between control and intervention periods (including in AKI severity) when patient demographics were analyzed at a hospital level; these data are available in Supplemental Material.

**Table 4. Results of multilevel logistic regression for mortality**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention (reference = control period)</td>
<td>1.04</td>
<td>0.91</td>
<td>1.21</td>
</tr>
<tr>
<td>Time (linear trend)</td>
<td>1.00</td>
<td>0.91</td>
<td>1.10</td>
</tr>
<tr>
<td>Season (reference = spring)</td>
<td>0.88</td>
<td>0.79</td>
<td>0.98</td>
</tr>
<tr>
<td>Autumn</td>
<td>1.03</td>
<td>0.91</td>
<td>1.17</td>
</tr>
<tr>
<td>Winter</td>
<td>1.13</td>
<td>1.04</td>
<td>1.22</td>
</tr>
<tr>
<td>Age group (reference = 60–69), yr</td>
<td>0.15</td>
<td>0.11</td>
<td>0.20</td>
</tr>
<tr>
<td>18–24</td>
<td>0.30</td>
<td>0.25</td>
<td>0.36</td>
</tr>
<tr>
<td>35–49</td>
<td>0.36</td>
<td>0.32</td>
<td>0.40</td>
</tr>
<tr>
<td>65–79</td>
<td>0.56</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Sex (reference = men)</td>
<td>0.86</td>
<td>0.80</td>
<td>0.92</td>
</tr>
</tbody>
</table>

The period in which the hospitals were exposed to the intervention compared with the control (reference) period is shown in the first row. Effects are seen with season, age, sex, and comorbidity, but there is no time effect on mortality over the study period. Cluster (hospital) was also included in the model. 95% CI, 95% confidence interval.

**AKI Progression**

AKI progression was assessed only in patients with AKI stage 1 or 2 at the time of AKI onset (21,672 AKI episodes). There was no significant effect of the intervention on AKI progression in the fully adjusted model (odds ratio, 0.94; 95% CI, 0.8 to 1.1; P = 0.40). These data are shown in Table 5. A total of 630 patients (2.6%) were coded as receiving acute RRT; the odds ratio of receiving RRT during the intervention period compared with the control period was 1.1 (95% CI, 0.8 to 1.6).
Sensitivity Analyses

Because of the effect of season on AKI incidence and outcome, we performed a sensitivity analysis to test the effect of the intervention on mortality during winter compared with other seasons by adding an interaction term to the model. We also explored whether time from a site’s initial exposure to the intervention was important. This tested whether an effect was sustained or diminished over time or if there were differences in the time required to reach maximal effect. Neither interaction showed differences in effect by season or time from exposure.

A sensitivity analysis for AKI progression was also performed that included patients with AKI stage 3 who progressed to RRT as well as those with AKI stages 1 and 2. This produced similar results to those of the primary analysis, with no significant difference between control and intervention periods.

**Process Outcomes**

Process measures were assessed in 1048 patients. Comparisons between control and intervention periods are shown in Figure 4. Care bundle usage increased from 0% to 40.2% from

<table>
<thead>
<tr>
<th>Quantile</th>
<th>Change in LoS (95% CI)</th>
<th>p-value</th>
<th>LoS at quantile (in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0 (-0.2 - 0.2)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0.2</td>
<td>-0.3 (-0.6 - 0.1)</td>
<td>0.3</td>
<td>4</td>
</tr>
<tr>
<td>0.3</td>
<td>-0.2 (-0.5 - 0.1)</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>0.4</td>
<td>-0.3 (-0.9 - 0.2)</td>
<td>0.08</td>
<td>8</td>
</tr>
<tr>
<td>0.5</td>
<td>-0.7 (-1.3 - -0.2)</td>
<td>0.04</td>
<td>10</td>
</tr>
<tr>
<td>0.6</td>
<td>-1.1 (-1.9 - -0.3)</td>
<td>0.03</td>
<td>13</td>
</tr>
<tr>
<td>0.7</td>
<td>-1.3 (-2.5 - -0.2)</td>
<td>0.03</td>
<td>17</td>
</tr>
<tr>
<td>0.8</td>
<td>-0.8 (-2.4 - 0.8)</td>
<td>0.7</td>
<td>24</td>
</tr>
<tr>
<td>0.9</td>
<td>-1.9 (-4.3 - 1.3)</td>
<td>0.2</td>
<td>36</td>
</tr>
</tbody>
</table>

**Figure 2.** Reduction in hospital length of stay in the intervention period, as shown by quantile regression analysis. LoS is shown on the y axis at different quantiles of the distribution. The solid line represents the estimated changes in LoS distribution quantiles from before to after the introduction of the intervention across the different quantiles of the distribution after adjustment for time, age, sex, co-morbid conditions, cluster (hospital), and seasonality, and the shaded area represents the 95% confidence interval (95% CI). Results show a reduced LoS during the intervention period (from quantiles 0.5 upward; effect size and median LoS at individual quantiles are shown in the table).

<table>
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<th>p-value</th>
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<tr>
<td>0.9</td>
<td>-1.0 (-2.1 - 0.13)</td>
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**Figure 3.** Reduction in AKI duration in the intervention period, as shown by quantile regression analysis. AKI duration is shown on the y axis at different quantiles of the distribution. The solid line represents the estimated changes in AKI duration distribution quantiles from before to after the introduction of the intervention across the different quantiles of the distribution after adjustment for time, age, sex, co-morbid conditions, cluster (hospital), and seasonality, and the shaded area represents the 95% confidence interval (95% CI). Results show a reduced AKI duration during the intervention period (from quantiles 0.8 onward; effect size and median AKI duration at individual quantiles are shown in the table).
control to intervention periods. Increases were also seen in AKI recognition (69.4% versus 88.8%), medication review (60.1% versus 71.3%), fluid assessment (74.4% versus 91.2%), and urinalysis (37.4% versus 64.7%). Changes in rates of specialist referral, renal imaging, and urinary catheterization were not seen. There were differences between sites in the degree of improvement and baseline levels of compliance; these data are included in Supplemental Figure 2.

**DISCUSSION**

In this multicenter SWCRT, a complex organizational-level intervention did not alter 30-day AKI mortality, but it did result in shorter duration of AKI episodes, a reduction in LoS, and improved AKI recognition. These findings were consistent across sensitivity and subgroup analyses.

Multiple reports from a variety of care settings consistently show that AKI in hospitalized patients is both common and associated with poor outcomes. In the absence of specific therapies, efforts to improve outcomes for patients have focused on increasing the consistency and quality of supportive care for AKI, exemplified by national and international campaigns, such as the International Society of Nephrology “0by25” campaign and the “Think Kidneys” national program in England. In parallel with these initiatives, there is a need to test the effectiveness of potential strategies and how they should be delivered across different health care systems. Our aim was to establish a more rigorous approach to this than previously used and evaluate an intervention aimed at improving AKI care within a multicenter, randomized study design. The pragmatic trial methodology allowed for adequate statistical power, with numbers of patients and event rates exceeding assumptions in the sample size calculation. Adherence to the allocated times for implementation was excellent across all five sites, and use of the UKRR infrastructure allowed the study to be undertaken efficiently and with independent data collection and analysis. The demographics of the study population were consistent with previous epidemiologic studies, and the higher AKI incidence and mortality in winter, recently described elsewhere, were important observations that required adjustment in statistical modeling and have relevance to the design of future studies. The SWCRT is a relatively novel trial design that is increasingly popular, particularly in the evaluation of complex interventions. It is more robust than before-after studies, because it allows for differentiation between the effect of the intervention and independent time-related factors (i.e., changes that would have happened anyway). In our study, because of the nature of the intervention, it overcame the problem of contamination of the control group (health care professionals within individual hospitals exposed to the intervention but treating patients in both control and intervention groups) that would have occurred with randomization at the patient level. SWCRTs are well suited to pragmatic aspects of the rollout of complex interventions, ethical issues are avoided if concerns about withholding an intervention in the control arm exist, and efficient trial design is possible. Disadvantages include the need for more complex statistical approaches (including those to avoid confounding) and biases that may arise if cluster size is too small; additionally, if individual patient data collection is required, that can lead to selection bias.

We did not observe any change in 30-day mortality, and this held true across a number of subgroup analyses. A previous single-center randomized trial showed that an isolated e-alert for AKI did not result in any change in physician behavior or patient outcomes. Our results differ in that we did observe improvements in AKI care delivery, including an increase in care bundle usage from zero during the control period to approximately 40% with the intervention. One interpretation of our results is that better AKI care does not translate into improved mortality, although an alternative explanation is that uptake of the intervention was incomplete across participating sites, whereas outcomes were measured on a hospital-wide basis. This would be supported by the bundle completion rates. Hence, even if an intervention is effective at changing provider behaviors, a challenge remains concerning spread and sustainability across an organization. Previous studies that have reported reductions in patient
mortality after complex interventions for AKI have generally used less robust methodology (e.g., before-after comparisons that cannot exclude effects of temporal trends on outcomes or limited statistical analysis); results from single-center studies may also be subject to attenuation of effect size when scaling this type of intervention to a larger number of sites. Our study was adequately powered to detect similar size reductions in mortality, although a recent study with a before-after design is notable for the very large sample size (64,000 patients) required to show a small but significant reduction in mortality with the introduction of computer decision support for AKI. In view of our findings, it may be advisable for future trials of complex interventions for AKI to consider alternative primary outcomes, particularly those that are organ specific (e.g., AKI duration and recovery of renal function) but that retain importance from a patient’s perspective. There was a beneficial effect of the intervention on LoS and AKI duration. The effect of the intervention on LoS was only apparent in those with a longer hospital stay. A similar pattern was seen with AKI duration, likely explained by limited potential for improvement in those with very short LoS or AKI duration. The positive effects of the intervention on LoS may be considered relatively modest for the individual patient, but given the very large numbers of patients who sustain AKI, this could translate into a significant health economic benefit; in England alone, it is estimated that there are >800,000 hospital admissions with AKI annually. Our post hoc analysis to

Figure 4. Improvements in processes of care with the intervention. Urinary catheterization was included as a balancing measure, and we did not observe an unintended increase in the proportion of patients catheterized for reasons other than relief of urinary obstruction.
examine the effect on AKI duration was undertaken to explore plausible reasons of how the intervention could directly reduce LoS. Its inclusion was further justified, because we were unable to study the effect of the intervention on another pre-specified secondary end point (critical care bed days). It is possible that the reduction in AKI duration may have a positive benefit on long-term patient outcomes, because AKI duration has been shown to be a very strong independent predictor of both subsequent CKD and long-term mortality.\textsuperscript{37,38} Unfortunately, reliable data collection to evaluate renal recovery in this study was not possible.

We also observed an increase in the incidence of AKI during the intervention period. This was not an effect of time or season. The most likely explanation is improved testing and recognition resulting from health care staff education. This is supported by the parallel increase in AKI diagnostic coding and the improvement in AKI recognition seen in the nested study of process measures. A similar effect has been reported in other studies.\textsuperscript{15} Importantly, in terms of interpreting the effect of the intervention on other outcomes, the increase in AKI incidence was seen equally across all stages of AKI, suggesting that improvements in LoS and AKI duration were not an artifact of a disproportionate increase in AKI stage 1 during the intervention.

There are some limitations of this study. The use of an electronic algorithm to identify patients with AKI may result in some misclassification of a small number of patients with AKI (e.g., progressive CKD).\textsuperscript{39} The inclusion of data from such patients may produce a small bias in favor of the null hypothesis. Using serum creatinine criteria without urine output may result in an underestimation of AKI incidence, but it was the only pragmatic approach for hospital-wide assessment of AKI, because the majority of patients do not have hourly urine output measurements. Results from analyses of secondary and exploratory outcomes were not adjusted for the effects of multiple testing and need to be interpreted in light of this fact. The potential for the change in AKI incidence to affect other outcomes should be noted, although we found no evidence to suggest that there was a shift toward less severe AKI in the intervention period, and we did not see any change in mortality that would be expected if severity of AKI was altered. The audit of process measures was conducted in a subgroup of patients, and therefore, no direct inferences can be drawn regarding these results and outcomes. The LIMS failure interrupted data collection for a short period, although this was successfully mitigated by extending the study duration. Finally, our findings may not be generalizable to other health care systems that differ substantially from the NHS in England.

In conclusion, a strategy to reduce avoidable harm associated with AKI did not alter 30-day AKI mortality. However, it was effective in reducing duration of AKI episodes and LoS, and it resulted in better AKI recognition. These results support a continued focus on improving the delivery of person-centered AKI care across acute specialties.

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DISCLOSURES

None.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2018090886/-/DCSupplemental.

Supplemental Figure 1. Quantile regression for change in hospital LoS (in days) with all patients included.

Supplemental Figure 2. Process measures presented individually per site.


Supplemental Table 1. Patient demographics in control and intervention periods at each hospital and overall.

Supplemental Table 2. Results of multilevel logistic regression for AKI incidence overall and for each AKI stage.

REFERENCES


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Supplementary material: contents

S1 Protocol 1
S2 Statistical Analysis Plan 16
S3 Methods: Case note audit data collection form and instructions 34
S4 Table: Patient demographics in control and intervention periods at each hospital and overall. 42
S5 Table: Results of multilevel logistic regression for AKI incidence, overall and for each AKI stage 43
S6 Figure: Quantile regression for change in hospital LoS (in days) with all patients included. 44
S7 Figure: Process measures presented individually per site. 45
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## Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project summary</td>
<td>3</td>
</tr>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>1.1  Background</td>
<td>4</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
</tr>
<tr>
<td>Project design</td>
<td>5</td>
</tr>
<tr>
<td>3.1  General design</td>
<td>5</td>
</tr>
<tr>
<td>3.1.1 Change methodology</td>
<td>5</td>
</tr>
<tr>
<td>3.2  Primary endpoints</td>
<td>6</td>
</tr>
<tr>
<td>3.3  Secondary endpoints</td>
<td>6</td>
</tr>
<tr>
<td>Methods</td>
<td>7</td>
</tr>
<tr>
<td>4.1  Subjects</td>
<td>7</td>
</tr>
<tr>
<td>4.2  Data collection</td>
<td>7</td>
</tr>
<tr>
<td>4.3  Flow diagram</td>
<td>11</td>
</tr>
<tr>
<td>Project procedures</td>
<td>12</td>
</tr>
<tr>
<td>5.1  Electronic AKI detection</td>
<td>12</td>
</tr>
<tr>
<td>5.2  AKI guidelines</td>
<td>12</td>
</tr>
<tr>
<td>5.3  Education package</td>
<td>12</td>
</tr>
<tr>
<td>5.4  Care bundle</td>
<td>12</td>
</tr>
<tr>
<td>Statistical plan</td>
<td>13</td>
</tr>
<tr>
<td>6.1  Sample size estimation</td>
<td>13</td>
</tr>
<tr>
<td>6.2  Statistical methods</td>
<td>13</td>
</tr>
<tr>
<td>Data handling and Record Keeping</td>
<td>13</td>
</tr>
<tr>
<td>7.1  Confidentiality</td>
<td>13</td>
</tr>
<tr>
<td>7.2  Source documents</td>
<td>13</td>
</tr>
<tr>
<td>Ethical considerations</td>
<td>14</td>
</tr>
<tr>
<td>Financial considerations</td>
<td>14</td>
</tr>
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<td>References</td>
<td>14</td>
</tr>
</tbody>
</table>
## Project summary

<table>
<thead>
<tr>
<th>Title</th>
<th>Tackling acute kidney injury - a multi-centre quality improvement project</th>
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| Protocol version and date | V5.1  
          October 2016 |
| Objectives | To upscale an effective package of interventions for Acute Kidney Injury (AKI) and to measure the impact of its introduction across several partner organisations (across two regional networks) representing the range of UK hospitals. |
| Methodology | Quality improvement project with stepped wedge design for introduction of interventions. The package of interventions will be introduced sequentially across each network, one centre per three month period. |
| Project duration | 30 months (including 6 month set up period) |
| Number of patients | Not defined – all patients sustaining AKI during the project lifespan will be included |
| Inclusion criteria | All hospitalised patients sustaining AKI in any of the partner organisations during the evaluation period of the project |
| Statistical methodology and analysis | We propose to evaluate the project on several different levels:  
  **Patient outcomes:**  
  Primary and secondary patient outcomes over each three month time period will be analysed, including effects for centre, time period and treatment variation between centres. A time series comparison between pre and post intervention periods will be made.  
  Primary outcomes:  
  - 30 day mortality in patients with AKI  
  Secondary outcomes:  
  - Incidence of hospital acquired AKI (h-AKI)  
  - Incidence of AKI progression  
  - Incidence of separate AKI stages  
  - Hospital length of stay (LoS) in patients with AKI  
  - Number of critical care bed days for patients with AKI  
  - Proportion of AKI patients with renal recovery by hospital discharge  
  **Standards of care**  
  Baseline and serial post-intervention audits (at each of the stepped wedges) of defined metrics of basic standards of care for patients who have sustained AKI.  
  **Qualitative evaluation of the intervention package**  
  Qualitative data about the utility and practicality of interventions will be collected, and will incorporate lessons learnt during the implementation process. |
1 Introduction

This is a service improvement project, which includes an extensive measurement component to allow assessment of the efficacy of the interventions. We have aligned the proposal to the NHS England AKI programme to promote ongoing sustainability beyond the life of this proposal, but also to provide a project template that is transferrable and can be used in other AKI quality improvement projects. Data collection and analysis will be established via data streams to the UK Renal Registry and University of Bristol within existing approvals from the Health Research Authority (previously National Information Governance Board).

1.1 Background

Acute Kidney Injury (AKI) is a sudden reduction in kidney function. It is common, harmful and often preventable, thus representing a major patient safety challenge for the NHS [1]. AKI occurs in as many as 10-15% of hospital admissions [2], usually in conjunction with other acute illnesses. Elderly patients and those with chronic conditions such as heart failure, diabetes and chronic kidney disease (CKD) are most vulnerable [3]. The presence of AKI dramatically increases severity of patients’ illness. Mortality rates of hospitalised patients with AKI are as high as 20-33% [4], whilst these patients are subject to longer, more complex hospital stays [5]. It is increasingly recognised that AKI also contributes to long term effects, in particular the development or progression of CKD [6].

As well as the adverse effects of AKI itself, there are many reports (in particular the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) Report) demonstrating that a significant component of the harm associated with AKI arises from poor standards of care [7]. It is also clear that only a minority of patients are cared for by nephrologists and AKI occurs regularly across all acute specialties. A major problem identified in the NCEPOD report were delays in diagnosis or even failure to recognise the presence of AKI, which often has a silent clinical course. Concurrently, it was demonstrated that early intervention focussed on basic elements of care can significantly improve the outcome of AKI [8]. It is therefore imperative that robust and scalable interventions are deployed to target these deficiencies.

2 Objectives

We propose to upscale an effective package of interventions for Acute Kidney Injury (AKI) and to measure the impact of their introduction across several partner organisations representing the range of UK hospitals. The aim is to improve the delivery of healthcare to patients with AKI that in turn will translate into better outcomes. We will assess the efficacy and the process of implementing the intervention on several levels:

1. **Impact on patient outcomes**
   A series of patient outcomes will be compared before and after introduction of the interventional package within a stepped wedge study design.

2. **Impact on quality of care delivered**
   Clinical audit of a series of defined metrics of basic care for patients who have sustained AKI

3. **Qualitative assessment of change process**
   Qualitative data from health care professionals (including members of the project team) will be used to evaluate practicality, acceptability and utility of interventions, whilst shared learning will allow ongoing tailoring of both the interventions and change methodology employed during implementation.
3 Project design

3.1 General design

This is a multi-centre quality improvement project using a stepped wedge design to sequentially introduce a package of interventions that has been trialled and shown to be successful at improving basic care and outcomes in patients who have sustained AKI in a single centre [9]. The interventions will comprise:

- An electronic AKI detection system based on biochemistry results and situated within pathology laboratory software, aimed at improving early recognition of AKI on a hospital-wide basis (section 5.1)
- An education programme to raise awareness and knowledge levels in all major medical and surgical specialities and across the range of healthcare workers (section 5.2)
- An AKI care bundle aimed at systematic improvements in the delivery of basic components of AKI care (section 5.3)

All patients sustaining AKI in the partner centres will be included; data collection will encompass a baseline measurement period before any change is instituted that will be compared with measurements after introduction of the package of interventions. Data collection will occur at each three month period of the stepped-wedge design in each partner organisation to provide additional methodological rigour over simple time-series comparisons. Baseline variation in current practice and differences in hospital characteristics (context) will be carefully recorded at project outset to allow subsequent assessment as to whether these differences impact on efficacy of interventions. Data collection and analysis will occur via links to the UK Renal Registry and University of Bristol, who will also provide expertise in change methodology and statistical support. NHS England will also provide partnership, and by aligning the proposal to the NHS England AKI programme board, we can demonstrate a realistic model to sustain change beyond the life of the proposal as well as a mechanism for wider scale adoption.

3.1.1 Change methodology

In addition to employing tried and tested interventions, their introduction will be supported by a structured approach to change management. This will be developed across each network of partner organisations (Yorkshire and Surrey) with arrangements for joint learning put in place. The detail of this will be tailored to each participating partner organisation but will consist of the following:

1. Planning stage, during which the following will be determined: profile of change characteristics, organisational attributes/characteristics profile, change management strategy, structure of local project teams, high level Trust engagement. There will also be a single learning event with representation from all partner organisations to refine the existing package of interventions. Pre-existing work from lead and partner organisations will be shared and discussed. From this, ideas will be shared and local versions of the most successful approaches to the interventions will be developed.
2. During the planning stage, the governance structure for the project will be settled, along with clear roles and responsibilities for key project team members.
3. Implementing change, of which there will be two main aspects:
   a. A peer-assist and peer-review programme. Centres at the start of implementation period will host a meeting during which their plans for implementing the interventions will be presented to team members from centres with experience (either the lead centre or centres ahead in the stepped wedge). With a challenge and confirm process, the following will be reviewed to maximise learning from prior experience (both explicit and tacit): where are you going to start; what formal/informal meeting structures exist to support the programme; measures intended; resources available and how they will be deployed; change methodology and expertise to support it; education plans; technology plans to support the project; how staff will be engaged; scope; timelines; risks how monitored
   b. At the end of implementation, a peer-review event will be held to include members from all centres, but in particular the next centre to implement in the stepped wedge. This will capture learning: What were our plans; What actually happened; What worked; What did we...
have to change; What would we have done differently; What are they key learning points to share with the next organisation.

b. Measurement for improvement. Use of run charts or statistical process control charts (SPC) to monitor frequently progress with delivery/uptake of interventions, particularly around introduction of the care bundle. This measurement is separate from the other aspects of evaluation.

4. In addition, other key components will be: communication plan, senior engagement and buy-in.

5. Reinforcement to sustain change e.g. post-intervention audit to look at uptake, corrective action plans, individual and group recognition approaches, success celebrations, end of project review

Rather than adopting a reactive response to resistance to AKI improvement measures, the aim is to engage and empower clinicians caring for patients with AKI. We aim to demonstrate the clinical need, instil a desire to participate and support the changes as well as making the necessary knowledge available. Ease of use of interventions will be an over-riding principle and the change management process will be integrated from the beginning of the project, being a major focus of the six month set up period.

3.2 Primary endpoints

Patient outcome measures are taken as the primary end points for this project. Comparisons will be within-cluster (pre- versus post-intervention) and between-cluster to estimate the treatment effect. This approach is necessary to avoid confounding the treatment effect with changes over time comparing baseline and post-intervention time periods. The primary outcome measures are defined as:

1. 30 day mortality rate in patients with AKI

3.3 Secondary endpoints

Secondary outcome measures are separated into three groups. Comparisons will be within-cluster (pre- versus post-intervention) and between-cluster to estimate the treatment effect for patient outcome and clinical audit measures.

Patient outcome measures:
1. Incidence of hospital acquired AKI (h-AKI)
2. Incidence of AKI progression (defined as AKI that increases by at least one stage from AKI stage at time of first detection)
3. Incidence of individual AKI stages (stage 1, stage 2 and stage 3)
4. Length of hospital stay of patients with AKI
5. Number of critical care bed days used by patients with AKI
6. Proportion of patients with AKI who achieve complete renal recovery by hospital discharge. Renal recovery will be defined as serum creatinine returning to a value less than 27µmol/l above baseline creatinine value.

Measures of basic care:
Clinical audit will be completed in each centre to assess the proportion of patients with AKI who receive a series of metrics of basic care.

Qualitative data:
Qualitative data about the utility and practicality of interventions will be collected from health care workers involved in the provision of care to patients with AKI and from project team members. Specific record of facilitators and barriers to implementation would be made, alongside successful solutions to aid subsequent dissemination. These data will be collected at each partner organisation in the following ways: Face to Face interviews or Focus groups, and SurveyMonkey style questionnaires. Depending on local resources, we will explore the possibility of using TurningPoint software to collect data before and after teaching sessions. Results will be complied and compared between partner organisations.
4 Methods

4.1 Subjects

All patients aged ≥18 years who sustain AKI at the participating centres during the project lifespan will be included. The incidence of AKI will be expressed per number of hospital admissions during each time period. For the purposes of this project, patients will defined as having AKI if they have an inpatient blood test that triggers an AKI Warning Stage test result, using the NHS England AKI detection algorithm ([http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf](http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf)). Hospital acquired AKI (h-AKI) will be defined as AKI that occurs >24hrs after hospital admission. Patients on long term dialysis will be excluded.

4.2 Data collection

All data used to assess the effectiveness of this project will be collected as part of routine clinical care. These data will be collected from electronic or paper hospital records without any additional patient interactions outside of that of routine clinical care.

**Patient outcome data:**

The following data points will be collected by setting up an IT report linking hospital outcome stay to electronic AKI detection results. It will also be acceptable to send separate files to the UKRR (for biochemical data and for hospital stay data) providing they both contain unique identifiers to allow subsequent linkage and removal of duplicates by the UKRR. A data specification will be issued to allow standardisation of data fields.

Data collection will need to occur when the results are suppressed (not visible to end-users during baseline periods) and when live in clinical practice (implementation periods). A report will be generated to cover each three month data collection period (as per figure below, section 4.3). Data collection will continue until each centre has completed two 3-month periods after the implementation phase. The report will include every patient aged 18 or over who has a hospital admission lasting ≥24hrs and with one or more AKI warning stage results generated from an inpatient serum creatinine concentration measurement. Depending on technical capabilities, ESRF patients will either be excluded based on dialysis clinical codes/unique monthly dialysis blood sets/location of blood samples (dialysis/renal unit).

Data set will include:

- Patient demographics: age at time of hospital admission, sex (male=1, female =0), ethnic group name/code
- NHS number (numerical field)/local identifier (text field)
- Date of admission (date field)
- Primary speciality (text field)
- Charlson co-morbidity score (numeric score) and constituent chronic disease binary scoring (1=present, 0=absent)*
- AKI data: initial AKI warning stage (numerical field limited to 1,2 or 3), highest AKI warning stage (numerical field limited to 1,2 or 3), time between admission and first AKI Warning stage result (numerical field, in hours), final inpatient creatinine result to assess recovery (numerical field, micromol/l)
- Hospital length of stay (numerical field, in days)
- ICU admission (1=admitted to ICU during hospital stay, 0=no ICU admission) and ICU admission length of stay (numerical field in days)
- In hospital mortality (numerical field, 1=died in hospital 0=survived to discharge)
- 30 day mortality (numerical field, 1=died within 30 days of first AKI warning stage result 0=survived to >30days)
- Date of death (date field)

- In addition, for each three month period, the total number of hospital admissions will need to be returned (= elective and non-elective admissions, excluding day case contacts and patient discharged directly from ED).
Acute myocardial infarction, cerebrovascular accident, congestive heart failure, Connective tissue disorder, Dementia, Diabetes, Liver disease, Peptic ulcer disease, Peripheral vascular disease, Pulmonary disease, Cancer, Diabetes complications, Paraplegia, Renal disease, Metastatic disease, Severe liver disease, HIV

**UKRR data submission:**
AKI warning stage data and serum creatinine concentration data will be submitted to the UKRR in line with the national guidance as per the following:

**Audit of basic standards of care:**
Sequential patients with AKI will be selected from designated audit periods, to include an equal number of patients with AKI stage 1, 2 and 3; AKI stage will be defined as maximum AKI stage during stay. Audit periods will consist of the final calendar month of each three month study period (1st baseline audit period May 2015). A list of all patients with AKI during these periods will be produced and used locally to select 30 patients at each centre (10 sequential cases for each AKI stage). Patients will be preferentially selected from the clinical areas in which the interventions are planned to or have been deployed with follow up audits in a similar hospital location.

Patients on a palliative care pathway will be excluded as will patients with End Stage Renal Failure on dialysis (NB patients with end stage renal failure with a renal transplant WILL be included). Audits will be carried out at baseline and then at each block of the stepped wedge period (total seven cycles per organisation, see figure below, section 4.3).

The following data points will be collected:
- Centre code
- Audit period (number field)
- Patient age (years), sex (male=1, female =0) plus other demographics as follows: ethnicity (as per NHS defn), NHS number, date of birth
- Date of admission (date field)
- Route of hospital admission (text field, limited list)
- First AKI stage during admission (number field limited to 1,2 or 3)
- Date of first AKI result (date field)
- Highest AKI stage during admission (number field limited to 1,2 or 3)
- Date of highest AKI result (date field)
- Ward descriptor of patient at time of AKI (text field, limited list)
- Duration of AKI
  a. Definition: number of days until serum creatinine returns to within 27micromol of baseline level for that individual
  b. Response options: 1 (=1-2days), 2 (=2-4days), 3 (= >4days), 99 (=not possible to define duration, e.g, creatinine not repeated, patient discharged prior to AKI resolution)
- Was AKI recognised?
  a. Definition: AKI recorded in hospital notes at any point during admission including discharge summary, use of AKI care bundle, investigation requested specifically for AKI
  b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)
- Was cause of AKI documented?
  a. Definition: cause of AKI recorded in hospital notes at any point during admission including discharge summary
  b. Response options: 1 (=yes), 0 (=no)
• If cause of AKI documented, enter all contributing factors as documented in hospital notes (text field)

• Was AKI care bundle used?
  a. Definition: AKI care bundle incorporated into patient record
  b. Response options: 0 (=no), 1 (=yes started within <6hrs), 2 (=yes started between 6-12hrs), 3 (=yes started between 12-24hrs), 4 (yes started between 24-48hrs), 5 (=yes started >48hrs), 6 (=yes but timing not known)

• Was AKI care bundle completed?
  a. Definition: All fields of AKI care bundle completed/signed for – this is an ‘all or none’ assessment
  b. Response options: 1 (=yes, 100% complete), 0 (=no, partially completed), 99 (=care bundle not utilised)

• Did the patient receive a fluid balance assessment?
  a. Definition: any one of: patient examination incorporating assessment of volume status (including euvolaemia), clinical impression that includes reference to volume status, treatment plan includes correction of over- or under- hydration
  b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)

• Did the patient receive urinalysis at time of or following AKI?
  a. Definition: urinalysis results recorded in medical or nursing record
  b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known), 99 (=not possible due to anuria).

Urinary ACR/PCR is not equivalent and should not be counted as an acceptable alternative

• Proportion of patients with AKI who were taking relevant medications at time of AKI* 
  a. Response options: 1 (=yes), 0 (=no) for each of the following:
  b. *Relevant medications: ACE inhibitor, ARB, MRA (e.g. spironolactone), NSAIDs, diuretics in setting of dehydration, aminoglycosides, trimethoprim

• Proportion of patients with AKI who have had medication review
  a. Definition: treatment plan includes cessation of relevant medication*, treatment plan includes avoidance of relevant medication, relevant medications stopped within 24hrs of first AKI warning stage result, documented pharmacy review
  b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)

• Proportion of patients with AKI stage 2 or 3 who receive renal imaging
  a. Definition: renal ultrasound/CT/MRI imaging following onset of AKI
  b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) 99 (=not appropriate – AKI stage 1 or senior clinician decision)
  c. If recording 99, state reason for coding as such (text field)

• Proportion of patients with AKI stage 3 who are discussed, referred to or seen by nephrology/ICU
  a. Definition: medical record contains documentation of telephone discussion with nephrology/ICU SpR or more senior, nephrology/ICU review or transfer to nephrology ward/ICU
  b. Response options: 1 (=yes, discussion with nephrology), 2 (=yes, referral to nephrology), 3 (=yes, discussion with ICU/outreach), 4 (=referral to ICU/outreach), 5 (=transfer to more specialist area; includes renal ward, high dependency or ICU), 0 (=no), 99 (=not appropriate – AKI stage 1 or senior clinician decision)

• In hospital mortality
  a. Definition: death during index hospital admission
  b. Response options: 1 (=died during admission), 0 (=survived to hospital discharge)

The audit will also include a process measure of care bundle usage and compliance. As well as a measure of implementation, this will also be used as a tool to promote ongoing usage of the care bundle. This will happen as part of the three monthly audit cycle of basic care, and will be the responsibility of the clinicians in each centre.
Other process measures:

- Number and type of educational interactions delivered at each site during each three month data collection period.
- Number of hits on local AKI guideline webpage in each three month data collection period. This will be used as a surrogate measure of AKI awareness in the organisation.

Qualitative data collection:

This will comprise of the following:

- Baseline questionnaire to be completed by each partner organisation prior to and during the design event to document context of their organisation and prior AKI work
- Recording implementation and validation of the AKI detection algorithm using the NHS England test script; this will evidence that each site is able to detect AKI and measure it in the same way. This will occur once at point of installation, supervised by lead biochemist in each organisation.
- Questionnaire/interview to be carried out with key personnel during implementation stepped wedge (therefore five in total)
- Depending on ethics approvals, we will explore widening this process to include frontline clinicians outside of the project team
- Review of transcripts/minutes of monthly project team teleconferences/meetings
- Collation of structured feedback from teaching sessions and on other educational materials (e.g. website, guidelines etc) and their interpretation within local context
- End of project interviews with project team members to record lessons for wider dissemination
- Results will be reviewed by participants to confirm and challenge (e.g. ‘is this your experience...’)

The focus of the analysis will be to identify patterns, themes, insights and understanding that will be organised into categories to aid presentation.
4.3 Flow diagram

Figure 1. Flow diagram showing step wedge design for implementation. *Data collection at each organisation will occur on a three monthly recurrence cycle including baseline (1-5 times depending on position in stepped wedge), implementation (1 time per centre) and post-implementation (1-5 times). At each timepoint, data will be collected on: three monthly AKI incidence and outcomes (pt outcome data), process (audit of care bundle usage and basic standards of care, and number/type of education sessions delivered)
5 Project procedures
The intervention package will be based on that implemented successfully at the lead centre. During the project planning stage, all centres will meet to share current experiences, review existing materials and refine these to maximise success in each partner organisation. Within this, there will be an ambition to standardise as much as possible. Variation in each of the interventions will be carefully documented throughout the life of the proposal.

5.1 Electronic AKI detection
Fully automated electronic AKI detection will be installed in the pathology Laboratory Information Management System (LIMS) at each participating centre. This algorithm will conform to the NHS England algorithm for the Early Detection of AKI (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf) and ensure compliance with the category 3 (directive) patient safety alert issued by NHS England in July 2014 (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki.pdf). This algorithm will generate a pathology test result (called AKI Warning Stage) for each creatinine result that is consistent with a diagnosis of AKI. This test result will be sent to each hospital’s results reporting system or patient management system as for any other biochemical test result, and in this way be communicated to the clinicians caring for that patient. The warning score will be accompanied by a text string giving advice to the clinician.

Local variation in enhancements to alerting process will be explored depending on capability (e.g. linkage to electronic prescribing or other more interactive alerting processes.). Each centre will decide locally as to whether AKI results will be telephoned to clinical areas, and at which stage of AKI this will occur.

5.2 AKI guidelines
Intranet guidelines for the diagnosis, management and referral of AKI will support the introduction of electronic detection at each centre. The number of hits on the webpage will be recorded (if possible) as one measure of AKI awareness. A sample guideline (that can be locally adapted) is included as an appendix.

5.3 Education package
Specific education programmes will be deployed as part of the intervention. This will have several components, including face to face teaching (both small and large groups) and e-learning. The programme will encompass the major acute medical and surgical specialities, all grades of clinician and other members of the health care team that provide care to patients with AKI. The number, type and audience of teaching sessions delivered will be recorded across each partner centre. Education materials already available in participating units will be reviewed and shared during the project set up period (e.g. e-learning package that can be viewed at http://www.uhl-library.nhs.uk/aki/). Sample education materials are included as appendices.

5.4 Care bundle
An AKI care bundle will be introduced at each centre alongside the detection and education elements of the intervention. The care bundle in use in the lead centre will be shared and then adapted for use in each partner organisation. The care bundles will be configured locally but will be based upon the following principles:

- Structured way of improving the care of patients
- Set of small, straightforward, evidence-based practices – generally three to five in total
- Occur at the same timepoint and in the same location
- Have to occur in totality (i.e. completing four out of five actions is non-compliant): compliance will be scored as all or nothing
- Clear accountability to ‘who owns it’ and ‘who delivers it’
- Use of ‘measurement for improvement’ approach to support introduction and ongoing usage
6   Statistical plan

6.1  Sample size estimation

Sample size calculations were performed by UK Renal Registry. Annual number of admissions for each institution were taken from HSCIC (total admissions across all partner organisations 434,000pa). A conservative assumption of AKI incidence of 2.5% of admissions and a mortality rate of 27.5% were made; in this setting a stepped wedge design with three month adoption periods would give >80% power to detect a relative reduction of 20% in 30d mortality. This is both clinically relevant (equating to 597 fewer deaths each year) and plausible.

6.2  Statistical methods

A full statistical analysis plan will be developed as a separate document.

7   Data handling and Record Keeping

7.1  Confidentiality

Information about patients will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Caldicott Guardian, individual Trusts’ IM&T Policy and the Health Research Authority. All audit data and hospital level patient outcome data will be stored on Trust password-protected computer/servers. Data transfer to the UKRR will occur within the UKRR’s comprehensive governance framework that is already in place, and will contain only those specific data items that have given approvals by the HRA. Patients will not be identifiable from any reports or publications that arise from this project.

7.2  Source documents

Source documents will include:

- Electronic hospital admission data
- Hospital notes
- Laboratory reports and electronic reports that are generated using AKI warning score
- Paper copies of audit forms
- Run charts/SPC charts as appropriate
8 Ethical considerations

This project uses interventions consistent with minimum standards of care as per the NHS England AKI programme workstreams; Derbyshire Research Ethics Committee has designated this proposal as quality improvement and waived the requirement for formal ethical approval and individual patient consent. Transfer and collation of patient data by the UK Renal Registry (UKRR) is approved by the Health Research Authority under section 251 of the NHS Act 2006. Ethical approval for the qualitative evaluation of staff will be sought from the University of Bradford ethical committee.

9 Financial considerations

Funding will be provided by the Health Foundation (Scaling Up Improvement call).

10 References

Statistical analysis plan for Tackling AKI Stepped Wedge Cluster Randomised Controlled Trial

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Table of contents:

Background page 3
Study design page 3
Intervention page 4
Outcomes Measures page 4
Randomisation and time-periods page 5
Sample size calculation page 7
Recruitment and randomisation page 7
Data source, collection and validation page 8
Potential problems page 10
Statistical analyses page 10
Timeline for analyses page 18
References page 18
List of abbreviation:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
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<td>AT</td>
<td>As treated</td>
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<td>CKD</td>
<td>Chronic kidney disease</td>
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<td>CRT</td>
<td>Cluster randomised trial</td>
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<td>HSCIC</td>
<td>Health and social care information centre</td>
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<td>ICC</td>
<td>Intra-cluster correlation</td>
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<td>Intensive care unit</td>
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<td>ITT</td>
<td>Intention to treat</td>
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<td>Patient administration systems</td>
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<td>Stepped-wedge cluster randomised trial</td>
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<td>United Kingdom Renal Registry</td>
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BACKGROUND

Acute Kidney Injury (AKI) is a sudden reduction in kidney function which is observed quite commonly during hospital stay, occurring in as many as 10-15% of hospital admissions [Wang et al., 2012]. It is harmful, and hospitalised patients with AKI have been shown to have longer, more complex hospital stays [Kerr et al., 2014], high hospital mortality rates [Selby et al., 2012] and higher risk of progression of CKD [Chawla et al., 2014].

The presence of AKI is also often recognised late or not at all, as it can have a silent clinical course and can present across many acute specialties so that not many patients developing AKI are seen by nephrologists.

It has been shown that a significant component of the harm associated with AKI arises from poor standards of care [NCEPOD report, 2009] and that early intervention focussed on basic elements of care can significantly improve the outcome of AKI [Balasubramanian et al., 2011]. It is therefore imperative that robust and scalable interventions are deployed to target these deficiencies.

While many patients are hospitalised with AKI already in progress (community acquired AKI), in many cases AKI develops during the hospital stay [hospital acquired AKI (h-AKI)].

This trial aims to deliver, across a range of UK hospitals, a package of interventions for Acute Kidney Injury (AKI) aimed to improve recognition and quality of care for AKI, and to assess how this translates into better outcomes in AKI patients and if this intervention can reduce the incidence of h-AKI (detailed protocol available on request).

For practical reasons this service can only be applied at the level of the population covered by the hospital and not on a subset of random patients within a hospital. Also the intervention is assumed to have a positive effect on AKI management/outcomes. For these reasons the study has been set up as a stepped-wedge cluster randomised trial (SWCRT), with the intervention applied at a cluster level and applied to all participating units by the end of the study. Such an approach overcomes any ethical problem of withholding a treatment considered likely to be effective, as the entire population recruited will receive the treatment by the end of the study. This approach also allows for differentiation between the effect of the intervention and potential independent unknown time-related factors.

There are no reporting guidelines specific to SWCRTs, so this Statistical Analysis Plan (SAP) is written to be consistent with the extension to cluster randomised trials of the CONSORT 2010 document [Campbell et al., 2012] and further suggestions recently published for SWCRT [Hemming et al, 2015]. This statistical analysis plan will guide the Trial Statistician during the statistical analysis of all quantitative outcomes in order to answer the objectives of the study.

STUDY DESIGN

A Stepped Wedge Cluster Randomised Trial approach will be taken. This means that the intervention will be delivered in sequential steps to one or more units of randomisation per time-period and
delivered to all the units of randomisation by the end of the study. This study has recruited 5 hospitals and is planned to take two years, between December 2014 and November 2016, with 2 initial control periods for all 5 hospitals, followed by 5 steps of randomisation (one hospital per step), and including a transition period (the first ‘treatment period’, when the treatment is expected not to have reached full efficacy on outcomes), for a total of 8 time-periods, each of 3 months in length (24 months in total – see Table-1, page.6).

THE INTERVENTION

The intervention (protocol, sections 3 and 5, available on request for details), has 3 parts:

- An AKI electronic detection system within pathology laboratory software
- An educational program to raise awareness and knowledge of AKI in care workers at hospital
- An AKI care bundle

The AKI electronic detection system has already been mandated at a national level (England only), with the plan to start nationwide from April 2015. The 5 hospital recruited for this SWCRT have been exempted from the initiative for the time being, so they would be able to wait to implement the intervention at their assigned time of randomisation, while having the electronic detection system in place since the end of 2014, but silent (as to measure the incidence of AKI during the baseline periods, with no active intervention).

OUTCOMES MEASURES

The outcomes of this study will be measured for all adult patients hospitalised overnight in the 5 participating hospitals, and identified as having an episode of AKI while in hospital by the pathology laboratory detection system (with results suppressed, non-visible to end-users, during control periods). The outcomes will be measured for the entire length of the study-period (1st Dec 2014 to 30th Nov 2016) for all of the AKI events, so multiple entries per patient are possible.

Primary outcome

- Thirty-day mortality after an episode of AKI. These are patient level data, binary outcome (0=patient alive 30 days after the AKI episode; 1=patient dead 30days after the AKI episode, logistic analysis).

Secondary outcomes

- 1. Incidence of h-AKI (aggregate data, counts, number of h-AKI cases, defined as AKI developed after >24hrs in hospital, with the denominator at risk being the total overnight hospitalisation episodes, Poisson analysis, standardised).
2. Incidence of AKI progression (defined as AKI that increases by at least one stage of AKI from AKI-stage at time of first detection) during hospitalisation. These are patient level data, binary outcome for each episode of AKI (0=did not progress during hospitalisation; 1=progressed during hospitalisation, logistic analysis).

As we will not be able to determine for all patients diagnosed with level-3 AKI if they progress to need of acute dialysis during hospitalisation, we will perform this analysis to the cohort of AKI level-1 and level-2 episodes only.

3. Incidence of individual AKI stages (stage 1, stage 2 and stage 3). These are aggregate data, counts, to analyse as secondary outcome n-1.

4. Length of hospital stay of patients with AKI (patient level data, counts in days, potentially to analyse using Poisson model, depending on the distribution of this outcome)

5. Number of critical care bed days used by patients with AKI (patient level data, counts of days in ICU for each patients, possibly to analyse using Poisson or negative binomial model zero inflated, depending on distribution, as many counts of zeros are expected.

6. Achievement of complete renal recovery by hospital discharge in AKI patients (with renal recovery defined as serum creatinine returning to a value less than 27μmol/l above baseline creatinine value). These are patient level data, binary outcome on all AKI patients (0=did not recover during hospitalisation; 1=recovered during hospitalisation, logistic analysis).

RANDOMISATION UNITS AND TIME-PERIODS

In this trial, the primary outcome will be measured for each episode of AKI detected in patients hospitalised overnight, while the intervention will be implemented at hospital level. Hence this is a cluster randomised trial, where the units of randomisation are the participating hospitals.

In this trial the intervention will be implemented in a total of 5 hospitals, with only one hospital being randomised each time at each step (with a total of 5 randomisation steps), with time periods of 3 months length.

This intervention is complex and would take some time to deliver it. While the electronic detection system has been set up in advance (with results kept suppressed at baseline) and can be activated immediately at start of intervention, teaching to staff will require some time as well as change in practice to be established. For these reasons we expect to observe no quantifiable effects on the outcomes of AKI patients at first after intervention, and hence we have planned to have a transition period. While data on primary and secondary outcomes will be collected for all periods of the study, data from the transition period for each hospital will be excluded from the analyses. As this trial has sufficient power, we have planned for the transition period to be of the same length as the unexposed/exposed time-periods (3 months).

In summary (see Table-1), we are planning to have, for each hospital, two or more control periods (unexposed to the intervention, coded as ‘0’), one transition period (the first period of intervention,
including the period of staff training, when exposure has started but no effect is expected because of need of a minimum length of time for the treatment to reach full efficacy, coded as ‘T’) and one or more exposure periods, when the intervention has already been delivered for ≥ 3 months (exposed to the intervention, coded as ‘1’).

A patient with AKI will be a ‘control patient’, a ‘transition-patient or a ‘treated/exposed patient’ depending on when and at which hospital the AKI episode occurs.

**Table 1** Scheme of timeline of trial.

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0=control, T=transition, 1=exposed

To define if the hospital has started the intervention in the assigned time frame, as per-protocol (PP), we will consider the date of activation of the pathology laboratory detection system (with results made active, visible to end-users). While ideally we expect the hospital to activate the system in the first week of the transition period, and to fully train the staff within these 3 months, we will consider the hospital as having followed the protocol as long as the date of activation of the detection system falls within the 3-months transition period assigned.

This study is not a longitudinal study of patients, but a study on repeated cross sectional data on patients that developed AKI in the same hospital, where patients included for each of the time-periods in the same hospital are usually different. Some of the patients could present more than once during a time-period (being hospitalised overnight and with an episode of AKI twice during 3 months) or could present with AKI multiple times in the same hospital but in different time periods. Correlation within patient will be accounted for in the analyses of AKI episodes’ outcomes if multiple episodes occur in a non-insignificant portion of patients.

This study can be viewed as a longitudinal study when considering aggregate data at the level of the hospital. The only aggregate-data outcomes that will be analysed are the incidence of h-AKI and the incidence of AKI separately by level of AKI, which will be repeated measurement at hospital level. The repeated nature of these measurements will be taken into account when investigating for changes in AKI incidence after intervention.
SAMPLE SIZE CALCULATION

The annual number of hospital admissions in the 5 institutions recruited was taken from HSCIC (total annual admissions of about 434,000). We used a conservative assumption of AKI incidence of 2.5% of admissions and 30-days mortality rate after AKI of 16% [Selby 2012], which corresponds to an average of AKI episodes per hospital per 3 months of about N=540. Power was set at 80%, alpha at 0.05 and a range of values for inter class correlation (ICC) between 0.01-0.2 was considered. For the sample size calculations we used a Stata program [Hemming and Girling, 2014], which can accommodate for the transition periods. This showed that with a trial study-time of two years (Dec’14 – Nov’16) using the 5 units, with one unit per randomisation step and with one transition period (as in table-1), we would be able to detect a decrease in mortality from 16% to 12.8%. This corresponds to a reduction of about 20% in 30-days mortality, which is both clinically relevant (equating to around 300 fewer deaths each year for the total of the 5 units) and plausible.

RECRUITMENT AND RANDOMISATION

- Eligibility of hospitals

Considering this trial was starting in parallel to the AKI national program (with the need to temporarily exempt the hospitals recruited) and the knowledge that the numbers of AKI episodes in hospitalised patients are fairly high, we planned to limit the recruitment to only 5 hospitals. For convenience the following 5 units were recruited, 2 from Surrey (Ashford and Frimley Park) and 3 from Yorkshire (Bradford, Leeds General and Leeds St. James).

- Eligibility of patients

Adult patients (>=18yrs) hospitalised overnight in the participating hospitals are eligible if they should present in hospital with AKI or develop an episode of h-AKI, during the study period. In particular, AKI will be identified by having an inpatient blood test that triggers an AKI warning stage result, using the NHS England AKI detection algorithm (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf), both in the control/baseline periods (when results are suppressed, not visible to end-users) and implementation periods.

Patients that are identified as having AKI but were already on chronic dialysis are not eligible and will need to be excluded, while patients with a renal transplant are eligible.

The five hospitals were recruited and the randomisation took place on the 11th of May 2015. Randomisation was performed using SAS-9.3 (RANUNI function), to generate 5 random numbers. These were then allocated to the five hospitals (listed in alphabetical order, based on hospital name), and finally the hospitals were sorted based on their random numbers, from smallest to highest, giving the sequence of randomisation.
DATA SOURCE, COLLECTION AND VALIDATION

Data from hospitals

All data used for the analyses described in this document will be collected as part of routine clinical care, from electronic hospital records. Patient level data will be extracted from the hospitals’ PAS for all patients flagged by the AKI electronic detection system. The data extracted will be sent to the UKRR. If data are sent in separate files, each file will need to contain unique patient identifiers to allow subsequent linkage and removal of duplicates by the UKRR.

Data set (see https://www.thinkkidneys.nhs.uk/wp-content/uploads/2014/12/AKI-Warning-Algorithm-Best-Practice-Guidance-final-publication-0112141.pdf for details) will include:

- Patient identifiers and demographics:
  - NHS number or Local Patient Identifier
  - Date of birth
  - Gender (M/F/U)
  - Ethnicity (name/code)
- Date of admission and date of discharge
- Primary specialty (text field)
- Charlson co-morbidity score (numeric score) and constituent chronic disease binary scoring (1=present, 0=absent)
- In hospital mortality (numerical field, 1=died in hospital 0=survived to discharge)
- 30 day mortality (numerical field, 1=died within 30 days of first AKI warning stage result 0=survived to >30 days)
- Date of death (date field)
- Length of hospital stay (numerical, in days)
- ICU admission (1=admitted to ICU during hospital stay, 0=no ICU admission) and ICU admission length of stay (numerical field in days)
- AKI data (see https://www.thinkkidneys.nhs.uk/wp-content/uploads/2015/01/Transmitting-AKI-Warning-Stage-Data-to-the-UKRR-final.pdf for detailed specification): initial AKI warning stage (numerical field limited to 1, 2 or 3), highest AKI warning stage (numerical field limited to 1, 2 or 3), time between admission and first AKI Warning stage result (numerical field, in hours), final inpatient creatinine result to assess recovery (numerical field, micromol/l).
- Data on population at risk: For each of the 3-months periods, the total number of hospital admissions in adult patients (≥18 yrs old, elective and non-elective admissions, excluding day case contacts and patient discharged directly from ED) will be needed to estimate the population at risk to analyse incidence of AKI. If possible, hospitals will return a file containing the full list of those admissions, without any patients’ identifier, but containing age (rounded to unit), gender and ethnicity of patients. This will allow the statistician to perform a standardised analysis of AKI incidence rates, without having to pre-specify to the hospitals the level of standardisation. If this is not possible, the total number of admission should be given.
preferentially by age-group (18-<25, 25-<30, 30-<35 and so on in 5-years age-bands), gender and ethnicity (South Asian, Black, Other (including mixed race and Chinese), White and Missing).

While the hospitals are responsible for identifying and excluding patients that were in day-care or were already receiving chronic dialysis, the data item ‘time between admission and first AKI Warning stage result’ will allow the analysts at the UKRR to distinguish episodes of community-acquired AKI and hospital-acquired AKI. Any hospital that should not be able to automatically apply the exclusion of those patients already on dialysis will need to provide the UKRR with necessary extra variables to identify these patients.

Hospitals will also need to let the UKRR know of any re-organisation of their laboratories during the study period, if this should occur. Such changes could cause an increase in the detected incidence of AKI, related to the cases of suspected-AKI. This trial does not analyse suspected-AKI (when an episode of AKI is suspected because of high values of creatinine but there are no baseline measurements). However, if links with new laboratories should occur during the study periods, and historical data are uploaded in the hospital lab-network, more baseline measurements could be available to the hospital and therefore the hospital would be able to appropriately flag more AKI episodes than previously, which could result in an apparent increase in incidence of AKI. If this should happen we will be able to investigate this as the AKI-dataset, providing the values of creatinine used in the e-alert, include a code of the lab that produced each specific data point. Also we expect to obtain from each hospital a measure of suspected-AKI for each time period. Using this information we could be able to adjust the analysis of incidence of AKI using a measure of incidence of suspected-AKI or alternatively we could exclude from the incidence analysis those AKI-episodes that were detected because of the new laboratory links. Best way to proceed will be decided once data are available, based on data completeness and reliability, if this event should occur.

Data collection from hospitals will occur every 3 months, to cover each 3month period. As the primary outcome is 30-day mortality, data for each period will be extracted with a minimum of 10 weeks delay (e.g. data for June-August 2015 will be extracted during the second half of Nov’15) or longer, depending on the capability of each hospital to update PAS.

Data from renal units
No data on acute or chronic RRT will be used in this analysis.
We would have preferred to include the need of acute dialysis or start of chronic dialysis during hospitalisation as a step of progression for AKI in the analysis of the secondary outcome n-2, but we were aware that information on acute dialysis would not have been complete, especially for those hospitals that do not have a renal unit within the hospital. As a consequence, we will not be using any information known to the UKRR on start of RRT in the analysis.
However, depending on completeness of patient identifiers such as NHS-number, the UKRR will perform a match of the patients with AKI with the RRT patients, available from the UKRR database. This will be done to validate the adherence to the exclusion criteria (exclude episodes of AKI from patient already on dialysis) applied by the hospitals before transferring the data to UKRR. The UKRR routinely collect data on RRT patients for all of UK, and by the summer of 2017 it should have the data on all RRT patients starting RRT up to Dec’16, which will cover the cohort of this study. Using the date of hospital admission and the date of RRT start in those patients matched, the analyst at UKRR will determine if any of the episodes of AKI included in the analysis occurred in dialysis patients, and exclude the appropriate episodes from the final analysis.

**POTENTIAL PROBLEMS**

- Missing data. ComPLEteness of patients’ demography from PAS is known to be high for age and gender, but we do expect missing data for the variable ‘ethnicity’. The outcome variables (AKI-level and changes, length of hospital stay and use of critical care beds) are expected to be complete, as well as mortality. If the percentage of entries with some missing demography data is low and appears to be distributed at random (with mortality equally distributed between set of data with complete covariates and set of data with some missing covariates) and if the power of the analysis is not compromised, we will perform the analysis restricting the cohort to AKI episodes with complete data. However, if the completeness of the variable ‘ethnicity’ should be too low, we will exclude this variable from the adjustment in all analyses and use the dataset with complete age/gender/comorbidity score. Multiple imputation will not be attempted as we don’t believe we have enough variables to perform a valid imputation.
- There is a risk that the time of implementation in some hospitals will slip. The impact of this will be explored in both a ‘per protocol’ and ‘as-treated’ secondary analysis.
- It is possible that a hospital will drop-out from the trial after being randomised (so no intervention at all). If this occurs, the impact will be explored in a per protocol analysis.

**STATISTICAL ANALYSIS**

Analyses of primary and secondary outcomes will be conducted at the UKRR in collaboration with the University of Bristol, using Stata MP12 and SAS 9.3.

**Number of participants**

We will present a table with number of total overnight hospitalisation episodes in adult patients, number of episodes of AKI (and numbers of patients with AKI episodes) and number of AKI episodes with complete set of variables, by hospital, per time-period (Table-2).
Table-2. Example of how numbers of AKI episodes and data completeness could be presented

<table>
<thead>
<tr>
<th>Hospital</th>
<th>N total overnight Hospitalisations</th>
<th>N episodes of AKI (N patients)</th>
<th>N hospitalisation with AKI and complete covariates (% of tot AKI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A TP_1</td>
<td>20,000</td>
<td>500 (450)</td>
<td>480 (96%)</td>
</tr>
<tr>
<td>TP_2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP_3</td>
<td></td>
<td>21000</td>
<td>580 (540)</td>
</tr>
<tr>
<td>TP_4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP_5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP_6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP_7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP_8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B TP-1</td>
<td>16,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP-2</td>
<td>15,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP-3</td>
<td>16,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP-5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

White=control; Orange=Transition; Yellow=exposed; 1 hospital per block, numbers for each time-period

TP=time period, 1=1stDec’14-28Feb’15, 2=1stMar-31may’15, and so on

**Interim analysis and data quality**

No interim analysis will be conducted on the primary and secondary outcomes. However data monitoring will be done to insure that the data collected by the hospitals via PAS are in the right format a first time by March 2016 from all of the 5 hospitals, and then again every 3 months for each of the hospitals.

We will also test the matching process of patients with AKI with the RRT patients in the UKRR database a first time in March 2016 and then again at the end of the study.

The last data collection should occur around Feb-Mar’17.

**Descriptive statistics**

The characteristics of patients with episodes of AKI by exposure (control versus intervention) and their outcomes will be presented for each hospital. We don’t expect significant differences in the demographic of the population feeding to each hospital during the 2 years study-period, and therefore the number of people presenting with AKI and needing hospitalisation is not expected to change with the intervention (as the incidence is determined by the AKI-alert activation in both baseline and exposed periods). However we hope to observe a decrease in h-AKI with the intervention, as this will hopefully increase awareness of AKI and use of protocols that minimise risks of AKI development.
Therefore when comparing the unexposed versus exposed patients with AKI, differences could be expected, if incidence of h-AKI should be influenced by the intervention differentially in specific subgroups of the hospitalised population (e.g. if h-AKI preventable in the younger but not in the older, then the post-intervention AKI population will be older).

Also, each hospital covers different population-mix, and while each one will contribute both control and exposed AKI-patients, they will do so in different proportions, depending on when they are randomised to the intervention. This will contribute greatly to any difference in demography between the control and the exposed groups.

Whilst we do not intend to test for differences in demography between control and exposed groups for the full cohort, we will adjust the analyses for the covariates described because of the potential imbalance across hospitals and across steps.

We will present categorical variables as numbers and percentages. Continuous variables will be presented using mean and standard-deviation, or median and interquartile range, depending on their distribution (see Table-3).

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Variable</th>
<th>Control</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>% male</td>
<td>N episodes (N patients)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Ethnicity</td>
<td>% male</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>age-group</td>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>comorbidity score</td>
<td>age-group</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>% AKI levels (1-2-3)</td>
<td>comorbidity score</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>% h-AKI over total AKI (or incidence of h-AKI)</td>
<td>% AKI levels (1-2-3)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>N deaths by 30days</td>
<td>% h-AKI over total AKI (or incidence of h-AKI)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Length hosp-stay (median-IQR)</td>
<td>N deaths by 30days</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>N Critical care (% &gt;0)</td>
<td>Length hosp-stay (median-IQR)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>N recovered (%)</td>
<td>N Critical care (% &gt;0)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>N progressed (%)</td>
<td>N recovered (%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>% male</td>
<td>N episodes (N patients)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Ethnicity</td>
<td>% male</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>age-group</td>
<td>Ethnicity</td>
<td></td>
</tr>
</tbody>
</table>

More detailed graphical representation of the primary outcome (30 day mortality) will be given (see Figure-1 for example). Summary results of secondary outcomes will also be presented in graphical or table format.
Analysis of primary outcome

The primary outcome (30 day mortality) is the only outcome that will be observed in a fixed time interval starting at date of admission rather than during the hospitalisation spell. While some hospitalisation spells will last one month or more, most will be shorter. As we have previously pointed out, multiple episodes (hospitalisations with AKI) in the same patient can occur. This is not a problem when the outcome is related exclusively to the hospitalisation spell (duration, ICU, recovery, progression). However in the analysis of 30 day mortality the presence of multiple episodes could create a problem, if the multiple episodes should occur within a month. For example a patient could be hospitalised with AKI for a week, return home and re-hospitalised a second time after a week, and die in hospital after few days, in which case the patient will be present twice in the cohort, both times with an outcome of death within 30 days. For this reason, only in this analysis, we will exclude repeated AKI-episodes that occur within a month from the previous hospitalisation, whichever the outcome. A case like the one just described will appear only once in the dataset, while a patient that is hospitalised with AKI for a week, then is back at home for 4 weeks, and then re-hospitalised with AKI again will appear twice.

Analysis of 30-day mortality will be done using a mixed-effects logistic regression, as a patient level analysis, and accounting for correlations between episodes in the same hospital by including hospital in the model as a random effect. If a non-insignificant proportion of episodes of AKI should be multiple episodes in same patients, we will also account for the correlation between episodes in the same patient by fitting a second random effect for patient in the analysis. The primary outcome response

Figure-1. Example of graphical presentation of 30-days mortality data for hospitals A and B, where empty symbol=control, pattern symbol=transition, full symbol=exposed.)
will be binary (patient died by 30days after AKI=1, patient still alive after 30days since AKI=0).
Mortality is expected to decrease after the intervention.

The odds ratio estimate of the mortality risk for the treatment effect (intervention versus control) with 95% confidence interval will be presented (Model-1). Analysis will be adjusted by time-period (step) (Model-2) and individual patients’ characteristics (Model-3) such as age at hospitalisation, gender, possibly ethnicity, and Charlson comorbidity score.

The impact of the intervention on outcomes could potentially change over time, as it could increase in time with increased experience of staff, but could also decrease after an initial improvement (as enthusiasm decrease/new staff not properly trained and so on) and therefore we aim to explore for possible interaction between time and treatment effect (Model-4).

The results from Model-3 will be considered the primary result, as the aim of this trial was to determine if any change after treatment in short-term mortality is related to the intervention and not to an independent calendar time trend, and since the primary outcome ‘mortality’ is highly correlated to age, the results adjusted by patient-demographic are believed to be the most appropriate.

**Model building**

Using the following notation:
- I clusters (i=1,2…5)
- M time points (j=1,2 ... 7)
- N episodes (k=1, 2 .....N), sampled per cluster per time point (cross-sectional cohort)
- Treatment indicator (Tij), equals 1 if intervention present at cluster I at time J, else it is 0.
- A fixed treatment effect (θ)
- Fixed time effect (γj) (one parameter if calendar time used as continuous variable, otherwise vector)
- Fixed effects [β] for patient-level demographics
- Patient-level adjustment variables [Xk]
- Random cluster effect (αi)
- Residual noise (εijk)

We will start with a unadjusted Before/After analysis of the effect of intervention (ignoring time effect)

**MODEL-1**

\[
\text{Logit } (Y_{ik}) = \theta \cdot T_{ij} + \alpha_i + \varepsilon_{ik}
\]

Where \( Y_{ik} \) = probability of the episode to have response=1 (death by 30-days after AKI)

\( \theta = \log \text{ odds for the treatment variable (1=exposed, 0=control) in centre I} \)
Then we’ll build in the effect of time-period (step) to investigate if any potential treatment effect is related only to the treatment or also to an independent effect of calendar time.

**MODEL-2**

\[
\text{Logit} (Y_{ijk}) = \theta^*T_{ij} + \gamma_j + \alpha_i + \epsilon_{ijk}
\]

Where \( \gamma \) = log odds for the effect of Time (vector if effect not linear)

Calendar time could be a potential confounder as other factors/events (e.g. other changes in NHS practice) could influence the outcome measure in both control and exposed patients. As this effect could be anything from absent, or gradual (progressive slow trend) to abrupt, (near simultaneous adoption of a new practice that has an immediate full-strength effect), calendar time will be fitted in the model first as categorical and then as a linear variable, and appropriate fitting will be chosen.

Then adjustment for patient-level characteristics at time of AKI-episode will be included in the model

**MODEL-3**

\[
\text{Logit} (Y_{ijk}) = \theta^*T_{ij} + \gamma_j + [\beta]X_{ijk} + \alpha_i + \epsilon_{ijk}
\]

Where \([\beta]\) = log odds for matrix of \(X\) covariates for the episode \(K\) in centre \(I\) at time \(J\)

The covariates of adjustment used in this analysis are the following: age at hospitalisation (linear or divided by age-group as needed), gender, possibly ethnicity, and Charlson comorbidity score.

Further to this, time will also be fitted as time since exposure (time as treatment effect modifier), to examine how the impact of the intervention develops over time (how long does it take to see a full size effect of the intervention over the primary outcome and if the size of the effect is maintained over time)

**MODEL-4**

\[
\text{Logit} (Y_{ijk}) = \theta^*T_{ij} + \gamma_j + [\beta]X_{ijk} + \omega Q_{ij} + \alpha_i + \epsilon_{ijk}
\]

Where \( \omega \) = log odds for the interaction between Time and Treatment (variable \(Q\), analysed as numerical variable (0=any control period, 1=1st exposure step, 2=2nd exposure step, etc.) for centre \(I\) at time \(J\). This will be fitted as continuous and categorical and the most appropriate fitting will be chosen.
The primary analysis will be performed on an intention to treat basis (ITT), with a unit considered to have followed the protocol if the e-alert system was activated within the 3months ‘transition period’ they were allocated to. As this is a complex intervention to roll out, some deviation from protocol is expected to occur. In this case also a per-protocol (PP) analysis and an as-treated (AT) analysis will be performed and all results will be presented.

For the PP analysis, we will exclude from the analysis the data collected during those time-periods where treatment did not coincide with that expected from the protocol (see table 4 for example).

**Table-4: PP analysis data exclusion**

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A-protocol</td>
<td>0</td>
<td>0</td>
<td>T</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A-as done</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>T</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A-data used</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

The as-treated analysis will include all cases of AKI as ‘control’ or ‘treated’ based on the treatment that patients had received at time of AKI episode, rather than the treatment they were assigned based on the allocation process. In this case 1st day of the month when e-alert was activated in each hospital will be considered the start of that hospital’s transition period.

The report will include adherence to the timing of randomisation to intervention.

NOTE: If a logistic model should not run/iterate then we will use an equivalent mixed-effects linear regression analysis, approximating by using 0 and 1 as a continuous variable for the dichotomous variable of 30 days mortality (Hussey and Hughes, 2007).

**Analysis of secondary outcomes**

- The aggregate-data secondary outcomes 1 and 3 (incidence of h-AKI and incidence of AKI by level of AKI - expressed as number of patients developing AKI per hospitalised population), will be analysed using a Poisson regression, standardised by age and gender and, if possible, by ethnicity.

This will be a cluster-level Poisson analysis, with one measure per time-period per hospital, if unadjusted (or one measure per time-period per hospital per age-gender subgroup, if standardised).

**MODEL**

\[
\log (Y_{ij}) = \log (\text{exposure}_{ij}) + \theta T_{ij} + \gamma_j + \alpha_i
\]

Where \( Y_{ij} = \text{count of AKI episodes in hospital } I \text{ at time } J \)
Exposure-ij=denominator, number of hospitalisations in hospital I at time J
θ = effect of the treatment variable (T=1 exposed, T=0 control) in centre I at time J
γ= effect of Time (vector if effect not linear)
(+ ωQij in the model if we want to investigate interaction between Time and Treatment)

- For secondary outcome n-2 (progression of AKI, binary outcome), we will use the same analysis as for the primary outcome (mixed-effect logistic regression), limited to the cohort of episodes classified as level-1 and level-2 AKI at time of first detection.
- The analysis of length of hospital stay (see outcome 4, page-5) in patients with AKI will be done with the model most appropriate to the distribution of this outcome. As these data are count data (days in hospital, integers >=1), Poisson analysis with episode-level data, adjusted for clustering at centre, is expected to be appropriate. However if the distribution should be approximate to normal or over-dispersion should be observed, mixed-effect linear regression or negative binomial models will be considered. The same model building sequence will be used as in the logistic analysis of the primary outcome.
- Number of critical care bed days (outcome 5, see page 5), will be analysed based on the distribution of the outcome. This is a count outcome, expected to be zero inflated, therefore a negative binomial analysis will be considered if over-dispersion is observed, or logistic regression if very little dispersion is observed for this outcome (0=No days in ICU, 1=one or more days in ICU).
- For secondary outcome n-6 (recovery of AKI, binary outcome, see page-5), we will use the same analysis as for the primary outcome (mixed-effect logistic regression). In this analysis, if patient should die during hospitalisation before recovery of function, the episode will be counted as a non-recovery, while if patient recovers renal function during hospital stay but then dies, the episode will still be considered as a recovery.
### TIMELINE FOR ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop statistical analysis plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomise units to steps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline period-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline period-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Transition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Transition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd Transition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th Transition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th Transition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last period, all on treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide 1st report on data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical analysis and write up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### REFERENCES


TACKLING AKI: AUDIT CASE REPORT FORM

AUDIT PERIOD (number from 1-7): 

HIGHEST AKI STAGE:  

Date of highest AKI stage:  

Demographic Data

NHS Number: 

Date of Birth:  

Ethnicity:

White:  

White British  

White Irish  

White Other  

Mixed race:  

White & Black Caribbean  

White & Black African  

White & Asian  

Other mixed background  

Asian or Asian British:  

Indian  

Bangladeshi  

Pakistani  

Other Asian background  

Black or Black British:  

Caribbean  

African  

Black Other  

Chinese or other ethnicity:  

Chinese  

Other  

Gender:  

Male  

Female  

Admission Data

Date of hospital admission:  

Route of hospital admission

Type:  

Elective  

Non-elective  

Source:  

Via ED  

Direct to admissions unit  

Direct to ward  

Transfer from other hospital  

Ward descriptor at time of AKI onset

ED  

Medical admissions unit  

Surgical admissions unit  

Nephrology ward  

Medical ward  

Surgical ward  

HDU  

ICU  

Other  
### AKI data

<table>
<thead>
<tr>
<th>Initial AKI stage:</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of initial AKI stage:</th>
<th>__ / __ / __ / __</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Duration of AKI</th>
<th>1-2 days</th>
<th>2-4 days</th>
<th>&gt;4 days</th>
<th>Not possible to determine</th>
</tr>
</thead>
</table>

### Was AKI recognised during hospital admission?

| No | ☐ |

<table>
<thead>
<tr>
<th>Yes:</th>
<th>Within 6hrs of AKI onset</th>
<th>☐</th>
<th>Within 6-12hrs of AKI onset</th>
<th>☐</th>
<th>Within 12-24hrs of AKI onset</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 24-48hrs of AKI onset</td>
<td>☐</td>
<td>&gt;48hrs of AKI onset</td>
<td>☐</td>
<td>Recognised but timing not known</td>
<td>☐</td>
</tr>
</tbody>
</table>

### Was cause of AKI recorded?

<table>
<thead>
<tr>
<th>Yes</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>☐</td>
</tr>
</tbody>
</table>

**If cause of AKI was recorded, enter causative factors as recorded in hospital notes (leave blank if cause of AKI not documented)**

### Patient outcome:

| Died during hospital admission | ☐ |
| Survived to hospital discharge | ☐ |
| Transferred to another hospital | ☐ |
### Process of care data

#### Was AKI care bundle used?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Within 6hrs of AKI onset</td>
</tr>
<tr>
<td>Yes:</td>
<td></td>
<td>Within 24-48hrs of AKI onset</td>
</tr>
</tbody>
</table>

#### Was care bundle completed in full:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Care bundle not utilised</th>
</tr>
</thead>
</table>

#### Did the patient receive a fluid balance assessment?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Within 6hrs of AKI onset</td>
</tr>
<tr>
<td>Yes:</td>
<td></td>
<td>Within 24-48hrs of AKI onset</td>
</tr>
</tbody>
</table>

#### Did the patient receive urinalysis at the time of or following AKI?

<table>
<thead>
<tr>
<th></th>
<th>No: Not done</th>
<th>Anuric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes:</td>
<td>Within 6hrs of AKI onset</td>
<td>Within 6-12hrs of AKI onset</td>
</tr>
<tr>
<td></td>
<td>Within 24-48hrs of AKI onset</td>
<td>&gt;48hrs of AKI onset</td>
</tr>
</tbody>
</table>

#### Was the patient receiving any of the following medications at time of AKI?

<table>
<thead>
<tr>
<th>Medication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
</tr>
<tr>
<td>MRA (e.g. spironolactone)</td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
</tr>
</tbody>
</table>
### Did the patient receive a medication review at time of or after AKI?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Yes:**
  - Within 6hrs of AKI onset
  - Within 6-12hrs of AKI onset
  - Within 12-24hrs of AKI onset
  - Within 24-48hrs of AKI onset
  - >48hrs of AKI onset
  - Yes but timing not known

### FOR AKI STAGE 2 AND 3 ONLY:

#### Did the patient receive renal imaging?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **No:** Not done
- **Yes:** Not done
- Not appropriate

- **Yes:**
  - Within 6hrs of AKI onset
  - Within 6-12hrs of AKI onset
  - Within 12-24hrs of AKI onset
  - Within 24-48hrs of AKI onset
  - >48hrs of AKI onset
  - Yes but timing not known

### FOR AKI STAGE 3 ONLY:

#### Did the patient receive specialist input (renal/ICU)

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **No:** Not done
- Not appropriate

- **Yes:**
  - Discussed with nephrology
  - Seen by nephrology
  - Discussed with ICU/CCOT
  - Seen by ICU/CCOT
  - Transfer to specialist area

* CCOT = critical care outreach team

### Balancing measure

#### Was patient catheterised as part of AKI care?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **No:** Not done
- Not possible (e.g. long term cathether)

- **Yes:**
  - To relieve obstruction
  - Yes, for any other reason including fluid balance monitoring

### Completed by:

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
## TACKLING AKI: AUDIT SUPPORT INFORMATION

| CENTRE CODE | FRI: Frimley  
BRA: Bradford  
ASP: Ashford and St Peters  
LGI: Leeds General Infirmary  
LSJ: Leeds St James’ |
|-------------|--------------------------------------------------|
| AUDIT PERIOD | Enter number corresponding to the audit period as below  
1. May 2015 (baseline)  
2. August 2015  
3. November 2015  
4. February 2016  
5. May 2016  
6. August 2016  
7. November 2016 (post intervention at all sites) |
| HIGHEST AKI STAGE DURING HOSPITAL ADMISSION | Number field either 1, 2 or 3  
*(placed at top of the form as 10 cases from each stage required for each audit period)* |
| DATE OF HIGHEST AKI STAGE | Date field: DDMMYYYY |
| NHS NUMBER | 10 digit number |
| DATE OF BIRTH | Date field: DDMMYYYY |
| ETHNICITY | As per NHS definitions |
| GENDER | Male or female (male=1, female =0) |
| DATE OF HOSPITAL ADMISSION | Date field: DDMMYYYY |
| ROUTE OF HOSPITAL ADMISSION | a) Elective (planned) admission =1 or Non-elective (emergency) admission =2  
b) Admission source: route via which patient entered hospital. Emergency Department (=1), Direct to Admission Unit (=2, either medical or surgical), Direct to ward without passing through ED or MAU/SAU (=3), Transfer from other hospital (=4) |
<table>
<thead>
<tr>
<th><strong>WARD DESCRIPTOR AT TIME OF AKI ONSET</strong></th>
<th>ED (=1), MAU (=2), SAU (=3), Nephrology ward (=4), General medicine ward (=5), High dependency (level 2) unit (=6), Intensive care unit (=7), General surgical ward (=8) Other (=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIAL AKI STAGE</strong></td>
<td>First AKI warning stage during hospital admission (as per NHS England AKI Warning Stage algorithm) i.e. AKI stage at onset of AKI. Number field either 1,2 or 3</td>
</tr>
<tr>
<td><strong>DATE OF INITIAL AKI STAGE</strong></td>
<td>Date field: DDMMYYYY</td>
</tr>
</tbody>
</table>
| **DURATION OF AKI**                    | a) Definition: number of days until serum creatinine returns to within 27micromol of baseline level for that individual. For the purposes of this audit, baseline defined as most recent stable creatinine level prior to AKI.  
   b) Response options: 1 (=1-2days), 2 (=2-4days), 3 (= >4days), 99 (=not possible to define duration, e.g, creatinine not repeated, patient discharged prior to AKI resolution) |
| **WAS AKI RECOGNISED DURING HOSPITAL ADMISSION?** | a) Definition: AKI recorded in hospital notes at any point during admission including discharge summary, use of AKI care bundle, investigation requested specifically for AKI  
   b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) |
| **WAS CAUSE OF AKI RECORDED?**         | a) Definition: cause of AKI recorded in hospital notes at any point during admission including discharge summary  
   b) Response options: 1 (=yes), 0 (=no) |
| **IF CAUSE OF AKI WAS RECORDED ENTER CAUSATIVE FACTORS** | Enter as recorded in the hospital notes ONLY (text field) |
| **DID PATIENT DIE DURING ADMISSION?**  | If patient died during index hospital admission: yes(=1), no(=0), transferred to another hospital (=2) |
| **WAS AKI CARE BUNDLE USED?**          | a) Definition: AKI care bundle incorporated into patient record  
   b) Response options: 0 (=no), 1 (=yes started within <6hrs), 2 (=yes started between 6-12hrs), 3 (=yes started between 12-24hrs), 4 (yes started between 24-48hrs), 5 (=yes started >48hrs), 6 (=yes but timing not known)  
   If the audit period is occurring before your centre has implemented the care bundle answer no for all cases. |
| **WAS THE AKI CARE BUNDLE COMPLETED?** | a) Definition: All fields of AKI care bundle completed/signed for – this is an ‘all or none’ assessment  
b) Response options: 1 (=yes, 100% complete), 0 (=no, partially completed), 99 (=care bundle not utilised)  
If the audit period is occurring before your centre has implemented the care bundle answer no for all cases. |
| **DID THE PATIENT RECEIVE A FLUID BALANCE ASSESSMENT?** | a) Definition: any one of: patient examination incorporating assessment of volume status (including euvoaemia), clinical impression that includes reference to volume status, treatment plan includes correction of over- or under-hydration  
b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (=yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) |
| **DID PATIENT RECEIVE URINALYSIS AT THE TIME OF OR FOLLOWING AKI?** | a) Definition: urinalysis (urine dipstick testing) results recorded in medical or nursing record  
b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (=yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known), 99 (=not possible due to anuria). **Urinary ACR/PCR is not equivalent and should not be counted as an acceptable alternative, urinalysis occurring before onset of AKI should not be counted** |
| **WAS THE PATIENT RECEIVING ANY OF THE FOLLOWING MEDICATIONS AT TIME OF AKI?** | Yes(=1) or No(=0) for each of the following classes of medications:  
a) ACE inhibitors e.g. ramipril; lisinopril; trandolopril; enalapril; captopril etc.  
b) Angiotensin receptor blockers e.g. candesartan; irbesartan; losartan; telmisartan; olmesartan; valsartan etc.  
c) Non-steroidal anti-inflammatory drugs (NSAID) e.g. ibuprofen; diclofenac; naproxen; indomethacin, meloxicam etc.  
d) Mineralocorticoid receptor blockers e.g. spironolactone; eplerenone  
e) Loop diuretic e.g. frusemide, bumetanide  
f) Thiazide diuretic e.g. bendrofluazide; indapamide; hydrochlorothiazide  
g) Aminoglycoside e.g. gentamicin; amikacin  
h) Trimethoprim |
| **DID THE PATIENT RECEIVE A MEDICATION REVIEW AT TIME OF OR AFTER AKI?** | a) Definition: treatment plan includes cessation of relevant medication*, treatment plan includes avoidance of relevant medication, relevant medications stopped within 24hrs of first AKI warning stage result, documented pharmacy review  
b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (=yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) |
| DID THE PATIENT RECEIVE RENAL IMAGING? | Not all AKI stage 1 patients need renal imaging, so score these patients as ‘no AKI stage 1’
| a) Definition: renal ultrasound/CT/MRI imaging following onset of AKI
| b) Response options: 0 (=not done), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (=yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) 98(=no AKI stage 1), 99(=not appropriate – AKI stage 1 or senior clinician decision) |
| DID THE PATIENT RECEIVE SPECIALIST INPUT? | Not all AKI stage 1 patients need renal imaging, so score these patients as ‘no AKI stage 1’/2
| Specialist input may be advice or review by nephrology, critical care outreach team (CCOT) or intensive care teams, or transfer to nephrology unit, high dependency or intensive care unit. If more than one of these happened, score that corresponding to highest level of input (transfer > seen by > telephone advice).
| a) Definition: medical record contains documentation of telephone discussion with nephrology/ICU SpR or more senior, nephrology/ICU review or transfer to nephrology ward/ICU
| b) Response options: 1(=yes, discussion with nephrology), 2(=yes, seen by nephrology), 3(=yes, discussion with ICU/outreach), 4(seen by ICU/outreach), 5(transfer to more specialist area; includes renal ward, high dependency or ICU), 0(=no), 99(=not appropriate – AKI stage 1/2 or senior clinician decision) |
| WAS PATIENT CATHETERISED AS PART OF AKI CARE? | Included as a balancing measuring (an increase in unnecessary urinary catheterization would be an unintended consequence)
| a) Definition: new urinary catheter placed as part of AKI management plan, or new urinary catheter placed within 48hrs of AKI onset
| b) Response options: Yes(=1 to relieve bladder outflow obstruction), Yes(=2 for any other reason including fluid balance monitoring), No(=0), Not possible(=99 e.g. long term catheter already in place, urinary diversion etc.) |
Table 4.2: Patient demographics in control and intervention periods at each hospital and overall.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Intervention Period</th>
<th>Control Period</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeds St James’ Hospital (LSJ)</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.2%</td>
<td>56.1%</td>
<td>54.2%</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>59.51</td>
<td>62.12</td>
<td>60.61</td>
</tr>
<tr>
<td>% of 0-10</td>
<td>1.5%</td>
<td>1.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>% of 11-30</td>
<td>7.0%</td>
<td>9.1%</td>
<td>7.9%</td>
</tr>
<tr>
<td>% of 31-60</td>
<td>88.2%</td>
<td>86.8%</td>
<td>87.5%</td>
</tr>
<tr>
<td>% of 61+</td>
<td>3.3%</td>
<td>1.7%</td>
<td>2.2%</td>
</tr>
<tr>
<td>% of South Asian</td>
<td>2.4%</td>
<td>5.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>% of Black</td>
<td>1.3%</td>
<td>2.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>% of White</td>
<td>95.0%</td>
<td>92.0%</td>
<td>94.0%</td>
</tr>
<tr>
<td>% of Deprivation</td>
<td>2.6%</td>
<td>3.3%</td>
<td>2.9%</td>
</tr>
<tr>
<td>% of Missing</td>
<td>85.3%</td>
<td>87.0%</td>
<td>85.9%</td>
</tr>
</tbody>
</table>

Note: The table above shows the distribution of patient demographics in control and intervention periods at each hospital and overall.
### Multilevel logistic regression for AKI incidence

<table>
<thead>
<tr>
<th>Intervention (reference=control): all cases</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention: AKI stage 1 only</td>
<td>1.13</td>
<td>1.03</td>
<td>1.25</td>
</tr>
<tr>
<td>Intervention: AKI stage 2 only</td>
<td>1.12</td>
<td>0.98</td>
<td>1.27</td>
</tr>
<tr>
<td>Intervention: AKI stage 3 only</td>
<td>1.11</td>
<td>0.95</td>
<td>1.28</td>
</tr>
</tbody>
</table>

**S5 Table: Results of multilevel logistic regression for AKI incidence, overall and for each AKI stage**
The effect size of an increase in AKI incidence with the intervention was very similar across all AKI stages; therefore a change in proportion of patients at different severities of AKI was not observed between control and intervention periods.
S6 Figure: Quantile regression for change in hospital LoS (in days) with all patients included. LoS is shown on the y-axis at different quantiles of the distribution, comparing the effect of the intervention against control period. The results are similar to the main analysis that included only those patients who survived to discharge. The solid line represents the estimated changes in LoS distribution quantiles from before to after the introduction of the intervention across the different quantiles of the distribution, and the shaded area represents 95% CI. Results show a reduced LoS during in intervention period (from quantiles 0.5 upwards, effect size and median LoS at individual quantiles shown in the table).
S7 Figure: Process measures presented individually per site.
Improvements were seen in care bundle utilisation, AKI recognition, fluid assessment and urinalysis rates. There were no differences in rates of renal imaging or specialist referral between control and intervention periods.

The x-axis shows the three-month periods sequentially throughout the study. Period 1 represents the baseline prior to any hospital introducing the intervention, periods 2-6 represent the intervention periods, and period 7 the post-implementation period with all hospitals exposed to the intervention.

For each hospital, the data point without shading shows the transition period at the start of implementation.

Abbreviations: Ashford: Ashford and St Peter’s Hospital; Bradford: Bradford Royal Infirmary; Frimley: Frimley Park Hospital; LGI: Leeds General Infirmary; LSJ: Leeds St James’ Hospital.