

# **An Organisational Level Programme of Intervention for Acute Kidney Injury: A Pragmatic Stepped-Wedge Cluster Randomised Trial**

*Running title: The Tackling AKI Study*

Nicholas M Selby<sup>1,2</sup>, Anna Casula<sup>3</sup>, Laura Lamming<sup>4</sup>, John Stoves<sup>5</sup>, Yohan Samarasinghe<sup>6</sup>, Andrew J Lewington<sup>7</sup>, Russell Roberts<sup>4</sup>, Nikunj Shah<sup>8</sup>, Melanie Johnson<sup>9</sup>, Natalie Jackson<sup>9</sup>, Carol Jones<sup>8</sup>, Erik Lenguerrand<sup>3</sup>, Eileen McDonach<sup>4</sup>, Richard J Fluck<sup>2</sup>, Mohammed A Mohammed<sup>4</sup>, Fergus J Caskey<sup>3</sup>

- 1 Centre for Kidney Research and Innovation, School of Medicine, University of Nottingham
- 2 Department of Renal Medicine, Derby Teaching Hospitals NHS Foundation Trust
- 3 UK Renal Registry & Translational Health Sciences, University of Bristol
- 4 University of Bradford
- 5 Bradford Teaching Hospitals NHS Foundation Trust
- 6 Frimley Health NHS Foundation Trust
- 7 Leeds Teaching Hospitals NHS Trust
- 8 Ashford and St Peter's NHS Foundation Trust
- 9 Yorkshire & Humber AHSN improvement academy

**Contact address:** Dr Nicholas Selby, Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Royal Derby Hospital Campus, Uttoxeter Road, Derby, DE22 3DT.

ORCID ID: 0000-0003-0351-8326

**Collaborators:** Mike Bosomworth, Georgie Duncan, Ashley Garner (Leeds Teaching Hospitals); Rifaq Azad (Bradford Teaching Hospitals); Bethany Bal, Arlene Batuista, Razya Hussain (Frimley Health NHS Foundation Trust); Erica Heppleston (Ashford and St Peters); Sally Benton, Craig McKibben (Surrey Pathology Services); Julie Slevin (UK Renal Registry);

**Contact email:** [nicholas.selby@nottingham.ac.uk](mailto:nicholas.selby@nottingham.ac.uk)

**Contact telephone:** 01332 724665

**Word count (excluding methods):** 2678 (abstract 263, methods 1820)

**Significance statement**

National and international guidelines recommend supportive approaches to acute kidney injury (AKI) management. Organisational strategies to improve delivery of AKI care have not previously been tested in multi-centre randomised studies. This paper describes a pragmatic, multi-centre, cluster-randomised study of AKI e-alerts, an AKI care-bundle and a programme of education across five UK hospitals. The intervention did not alter the primary outcome of 30-day mortality but did result in improvements in hospital length of stay, a reduction in AKI duration and an increase in AKI incidence reflecting improved recognition. These results in combination with previous evidence show that strategies to improve the systematic delivery of supportive AKI care can lead to improvements in patient outcomes.

## **Abstract**

*Background:* Variable standards of care may contribute to poor outcomes associated with acute kidney injury (AKI). We evaluated whether a multifaceted intervention (AKI e-alerts, an AKI care bundle and an education programme) would improve delivery of care and patient outcomes.

*Methods:* A multi-centre, pragmatic, stepped-wedge cluster randomised trial (SWCRT) was performed in five UK hospitals. The intervention was introduced sequentially across fixed three-month periods until all hospitals were exposed. The intervention schedule was randomly determined. All patients with AKI aged  $\geq 18$  years were included. 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.

*Findings:* 24,059 AKI episodes were studied. Overall 30-day mortality was 24.5%, with no difference between control and intervention periods (OR 1.04, 95% CI 0.91-1.21). Hospital length of stay (LoS) was reduced with the intervention (-0.2days (95% CI -0.5 to 0.1), -0.7days (-1.3 to -0.2) and -1.3days (-2.5 to -0.2) at the 0.3, 0.5 and 0.7 quantiles respectively). AKI incidence increased (adjusted incidence rate ratio 1.12, 95% CI 1.03-1.22) with a parallel increase in the proportion of patients with a coded diagnosis of AKI. Process measures were assessed in 1048 patients, with improvements seen in several metrics including AKI recognition, medication optimisation and fluid assessment.

*Conclusions:* A complex, hospital-wide intervention to reduce harm associated with AKI did not alter 30-day AKI mortality but did result in reductions in LoS, accompanied by improvements in in quality of care. AKI incidence increased, likely reflecting improved recognition.

## **Introduction**

Acute kidney injury (AKI) is common and is associated with markedly elevated short-term morbidity and mortality, subsequent risk of chronic kidney disease (CKD) and large increases in healthcare resource utilisation.<sup>1</sup> AKI occurs in 5%–22% of hospital admissions and mortality rates exceed 20%, rising to greater than 50% in those most severely affected.<sup>2</sup> In the absence of specific therapies, AKI management requires methodical delivery of basic elements of care.<sup>3</sup> Despite universal recommendation of this approach in national and international guidelines,<sup>4-6</sup> successive reports have described variation in the quality of clinical care for AKI, with poor standards of care associated with worse outcomes.<sup>7-10</sup> Whilst there are no proven interventions for AKI, the evidence-base to support organisational level interventions to address variations in AKI care is also lacking. In the only previous randomised trial, a text message alert for AKI did not change physician behaviour or patient outcomes, possibly because the alert was introduced without recommendations for care or other interventions.<sup>11</sup> Conversely, several non-randomised 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.<sup>12-15</sup> Additionally, all but one of these studies are single-centre, so do not inform whether successful interventions retain effectiveness if scaled to other organisations. We therefore sought to address some of these knowledge gaps by performing a multicentre, randomised trial to test the hypothesis that a complex intervention for AKI (comprising AKI e-alerts, an AKI care bundle and a programme 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 multi-centre, pragmatic stepped-wedge cluster randomised trial (SWCRT). The study was conducted using a published protocol,<sup>16</sup> which was consistent with the extension to cluster randomised trials of the CONSORT 2010 document<sup>17</sup> and recommendations for SWCRTs.<sup>18</sup> The protocol and statistical analysis plan were published on the NHS England Think Kidneys Programme website<sup>19</sup> and are included in Supplementary Material.

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

The intervention, designed to reduce avoidable harm associated with AKI, was introduced across five National Health Service (NHS) hospital sites representing academic and non-academic centres as well as those with and without onsite nephology 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 three-month periods until all five hospitals were exposed to the intervention (Figure 1). A six-month baseline period prior to any of the sites introducing the intervention was followed by five three-month implementation steps (one hospital per step). The three-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 three-month period of exposure to the intervention following the transition period.

We included all patients aged  $\geq 18$  yrs who were hospitalised 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,<sup>20</sup> 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 seven days, or a median of values from the preceding 8-365 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 end-stage kidney disease. 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 UK Renal Registry (UKRR) was approved by the Health Research Authority under section 251 of the NHS Act 2006.

### *Randomisation and blinding*

The unit of randomisation (the cluster) was the participating hospital. Randomisation was performed by the UK Renal Registry (UKRR) and took place on the 11<sup>th</sup> 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. Due to 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 international guidelines.<sup>4-6, 21</sup> The components of the intervention were:

- An AKI electronic detection and alerting system,
- An AKI care bundle, containing individual elements pertaining to assessment, investigation and basic management of AKI (summarised in Table 1A),<sup>22</sup>
- An educational program to raise awareness and knowledge of AKI in healthcare workers (summarised in table 1B).

Introduction of the intervention was supported by a structured approach to change management, described elsewhere.<sup>16</sup> This included permissive tailoring of the elements of the intervention to fit each hospital's local context, but the same basic elements were present across all sites. The electronic AKI detection system was uniform across all sites, conforming with a nationally mandated specification.<sup>20</sup> Audit during the set up 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 randomised to introduce the intervention. The alert message notified the healthcare professionals that the patient had sustained AKI, the stage of AKI and included an advice message advising a clinical response/review of the patient and sign-posting of local AKI resources (guidelines, 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 1A) although initial care bundle content and design was refined in response to end-user feedback during the first three 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 that were integrated into patients' hospital notes apart from one centre 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 included the development of educational materials, e-learning and awareness raising. Formal teaching sessions were typically delivered using PowerPoint presentations, whilst ad hoc or opportunistic teaching on wards were focussed around real time patient examples or signposting project resources. A summary of educational activities that were delivered in each hospital is shown in table 1B.

The intervention was delivered by an AKI project team at each hospital, which consisted of staff provided by the central team (project managers CJ, NJ, MJ), principle investigators (YS, NS, AJL, JS, RR) 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. Pre-defined secondary outcomes included: incidence of hospital acquired AKI; AKI progression to higher stages; incidence of individual AKI stages; and length of hospital stay (LoS).<sup>16</sup> We defined hospital acquired AKI as that with its onset >24hrs after hospital admission, and AKI progression as an increase of  $\geq 1$  AKI stage from time of detection.<sup>23</sup> Following 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 pre-specified secondary endpoints (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 (PAS) to determine patient identifiers and demographics, date of admission and discharge, all diagnosis codes from the index admission (as per International Classification of Diseases, 10<sup>th</sup> Revision (ICD-10) and Charlson co-morbidity score)<sup>24</sup> and date of death. These data were transferred directly to the UKRR from each site independently of the study teams and were analysed 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 three-month period for total number of adult admissions grouped by age, gender and ethnicity to allow calculation of AKI incidence. In September 2016, there was an IT 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

an extra period of data collection (Dec 2016–Feb 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, care bundle usage), as determined by repeated cycles of clinical audit (30 sequential patients per site from each three-month data collection period, giving a planned sample of 1050 case notes evenly distributed across AKI stages 1, 2 and 3). A standard data collection form and data specification sheet were used; these are included as Supplementary Material.

#### *Sample size calculation*

An *a-priori* sample size calculation was undertaken.<sup>25</sup> The total number of annual hospital admissions across the five sites (434,000) was taken from the Health and Social Care Information Centre ([www.hscic.gov.uk](http://www.hscic.gov.uk), April 2014-March 2015). The most conservative published rates for assumptions of the proportion of hospital admissions with AKI (2.5%)<sup>26</sup> and 30-day mortality (16%)<sup>27</sup> were used. Power was set at 80%, alpha at 0.05 and a range of values for intra-cluster correlation between 0.01-0.2 were considered. With a trial study-time of two years, five participating sites (one per randomisation step), one transition period per site and the design effect of the SWCRT,<sup>25</sup> we calculated that to detect an absolute decrease in 30-day-mortality of 3.2%,<sup>12, 13</sup> 10,850 AKI episodes should be studied.

#### *Statistical analysis*

Analysis of 30-day mortality was undertaken using multilevel logistic regression at the individual patient level with hospital modelled as a random effect, and adjusting for time, patients' co-variables (age, gender, comorbid conditions), and the effect of seasonality. We pooled time into quarterly intervals, treated as equally spaced in analytic models. Only first hospitalisations 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 control period.

Secondary analyses were also undertaken at the individual patient level, again adjusting for time, patients' co-variables (age, gender, comorbid conditions), cluster (hospital) and the effect of seasonality. AKI incidence was calculated using the total number of overnight hospitalisation episodes within each time period as the denominator, and analysed using multilevel negative-binomial regression. AKI progression was analysed as a binary outcome for each overnight hospitalisation episode using multilevel logistic regression as for the primary outcome (excluding AKI stage 3). The hospital length of stay (LoS) and AKI duration data were highly skewed, and the fit of prespecified Poisson and negative binomial regression



models were poor (inadequate correlation between observed versus predicted values). Therefore, quantile regression models were fitted to allow comparisons at points across the whole distribution (after adjustment for age, gender, comorbid conditions, time, season, centre) 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.<sup>28,29</sup> 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/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, and 12,507 episodes (52%) were hospital-acquired. Patient demographics in control and intervention periods are shown in Table 2, and data for individual hospitals in Supplementary Material. 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 randomisation 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-February) of 1.08, 95% CI 1.02-1.13,  $p=0.006$  as compared with spring (March-May)). Outcome analyses were adjusted for these co-variables.

### *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 3), the odds ratio for 30-day mortality in the intervention period versus the control period was 1.04 (95% CI 0.91-1.21,  $p=0.55$ ). 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 as compared to the control period (incidence rate ratio (IRR) 1.12, 95% CI 1.03-1.22,  $p=0.009$ ). The same effect size was observed across each stage of AKI when analysed separately (Supplementary Material). 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 IRR 1.27, 95% CI 1.15-1.39,  $p<0.001$ ), suggesting improved AKI recognition.

### *Hospital length of stay (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

(IQR 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 upwards). At the 0.5 quantile, the effect size was a reduced length of stay 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 including all admissions regardless of whether or not the patient was alive at discharge, the same pattern of results was observed (Supplementary Material).

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 (IQR 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,  $p=0.01$ ).

Quantile regression was chosen in place of the pre-specified analyses for LoS and AKI duration as 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 quantile regression: with Negative Binomial regression, LoS was decreased in the intervention period by 6.6%, 95% CI 1.3-11.6%,  $p=0.015$ ; with Poisson regression LoS was decreased by 6.2%, 95% CI 4.7-7.7%,  $p<0.001$ ; with Negative Binomial regression, AKI duration decreased by 14.7%, 95% CI 8.8-20.3%,  $p<0.001$ ; and with Poisson regression AKI duration decreased by 14.0%, 95% CI 11.4-16.5%,  $p<0.001$ .

#### *AKI progression*

AKI progression was assessed only in patients with AKI stage 1 or 2 at time of AKI onset (21,672 AKI episodes). There was no significant effect of the intervention on AKI progression in the fully adjusted model (OR 0.94, 95% CI 0.8-1.1,  $p=0.4$ ). These data are shown in Table 4. A total of 630 patients (2.6%) were coded as receiving acute renal replacement therapy (RRT); the odds ratio of receiving RRT during the intervention period as compared to the control period was 1.1 (95% CI 0.8-1.6).

#### *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 as compared to 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 the primary analysis, with no significant difference between control and intervention periods.

#### *Process outcomes*

Process measures were assessed in 1,048 patients. Comparisons between control and intervention periods are shown in Figure 4. Care bundle usage increased from 0% to 40.2% from 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 catheterisation were not seen. There were differences between sites in the degree of improvement and baseline levels of compliance; these data are included in Supplementary Material.

## Discussion

In this multi-centre, stepped-wedge cluster randomised trial, a complex organisational-level intervention did not alter 30-day AKI mortality, but did result in shorter duration of AKI episodes, a reduction in hospital length of stay and improved AKI recognition. These findings were consistent across sensitivity and sub-group analyses.

Multiple reports from a variety of care settings consistently show that AKI in hospitalised patients is both common and associated with poor outcomes.<sup>30, 31</sup> In the absence of specific therapies, efforts to improve outcomes for patients have focussed 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 programme in England.<sup>21, 32</sup> 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, and evaluate an intervention aimed at improving AKI care within a multicentre randomised study design. The pragmatic trial methodology allowed adequate statistical power, with numbers of cases 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 epidemiological studies,<sup>27, 33</sup> and the higher AKI incidence and mortality in winter, recently described elsewhere,<sup>34</sup> was an important observation that required adjustment in statistical modelling and has 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 as 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, due to the nature of the intervention, it overcame the problem of contamination of the control group (healthcare professionals within individual hospitals exposed to the intervention but treating patients in both control and intervention groups) that would have occurred with randomisation at the patient level. There are other advantages; SWCRTs are well suited to pragmatic aspects of the roll-out 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), biases that may arise if cluster size is too small; and if individual patient data collection is required that can lead to selection bias.<sup>18</sup>

We did not observe any change in 30-day mortality, and this held true across a number of subgroup analyses. A previous single-centre randomised trial demonstrated that an isolated e-alert for AKI did not result in any change in physician behaviour or patient outcomes.<sup>11</sup> 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 behaviours, a challenge remains concerning spread and sustainability across an organisation. Previous studies that have reported reductions in patient mortality following 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-centre 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 demonstrate a small but significant reduction in mortality with the introduction of computer decision support for AKI.<sup>15</sup> However, our study was more than double the estimated sample size and we did not observe any trend towards mortality reduction. The primary endpoint of 30-day mortality was chosen based on previous single centre quality improvement studies that did show improvements in this outcome.<sup>12, 13</sup> However, mortality associated with AKI is driven by multiple factors, including effects of co-morbidity and co-existing acute illness in addition to effects from AKI.<sup>35</sup> In view of our findings, it may be advisable for future trials of complex interventions for AKI to consider alternative primary outcomes, particularly those which are organ-specific (e.g. AKI duration, recovery of renal function) but which retain importance from a patient's perspective.

There was a beneficial effect of the intervention on hospital length of stay 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.<sup>36</sup> Our post hoc analysis to examine the effect on AKI duration was undertaken to explore plausible reasons by which the intervention could directly reduce LoS.

Its inclusion was further justified as we were unable to study the effect of the intervention on another prespecified 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 as AKI duration has been shown to be a very strong independent predictor of both subsequent CKD and long term mortality.<sup>37, 38</sup> 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 healthcare 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.<sup>15</sup> 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 artefact 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 AKI cases may result in some misclassification of a small number of patients with AKI (e.g. progressive CKD).<sup>39</sup> The inclusion of data from such patients may produce a small bias in favour of the null hypothesis. Using serum creatinine criteria without urine output may result in an under-estimation of AKI incidence, but was the only pragmatic approach for hospital-wide assessment of AKI where 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. 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 towards less severe AKI in the intervention period, nor did we see any change in mortality which 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 generalisable to other healthcare systems that differ substantially from the National Health Service in England.

In conclusion, a strategy to reduce avoidable harm associated with AKI did not alter 30-day AKI mortality but was effective in reducing duration of AKI episodes and hospital length of

stay, and resulted in better AKI recognition. These results support a continued focus on improving the delivery of person-centred AKI care across acute specialities.

### **Acknowledgments**

We would like to thank and acknowledge the input of Mr Peter Naish and Dr Clare Corps, who as patient representatives provided valuable insights during study design and delivery.

### **Financial Disclosures**

This study was funded by a grant from the Health Foundation (award number 1502-Derby-Selby-SUI). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no competing interests to declare.

### **Author contributions**

All authors have been involved in the drafting and final approval of this article and agree to be accountable for the aspects of the work to which they contributed. In addition, authors had the following roles:

- Nicholas M Selby: Study conception, design and overall study management, data analysis and interpretation of results,
- John Stoves; Yohan Samarasinghe; Andrew J Lewington; Russell Roberts; Nikunj Shah; Melanie Johnson; Natalie Jackson; Carol Jones: Study delivery and data acquisition,
- Anna Casula; Fergus J Caskey: Study design, production of statistical plan, data collection and analysis,
- Erik Lenguerrand: Study design, production of statistical plan, data analysis,
- Laura Lamming; Eileen McDonach; Mohammed A Mohammed: Study design, data collection and analysis,
- Richard J Fluck: Study conception and design, overall study management.



## Supplementary Material Table of Contents

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

## References

1. Lameire, NH, Bagga, A, Cruz, D, De Maeseneer, J, Endre, Z, Kellum, JA, Liu, KD, Mehta, RL, Pannu, N, Van Biesen, W, Vanholder, R: Acute kidney injury: an increasing global concern. *Lancet*, 382: 170-179, 2013.
2. Selby, NM, Fluck, RJ, Kolhe, NV, Taal, MW: International Criteria for Acute Kidney Injury: Advantages and Remaining Challenges. *PLoS Med*, 13: e1002122, 2016.
3. Vanmassenhove, J, Kielstein, J, Jorres, A, Biesen, WV: Management of patients at risk of acute kidney injury. *Lancet*, 389: 2139-2151, 2017.
4. KDIGO AKI Work Group: Clinical Practice Guideline for Acute Kidney Injury. *Kidney inter, Suppl*, 2: 1-141, 2012.
5. Lewington, A, Kanagasundaram, S: Renal Association Clinical Practice Guidelines on acute kidney injury. *Nephron Clin Pract*, 118 Suppl 1: c349-390, 2011.
6. Ftouh, S, Thomas, M, Acute Kidney Injury Guideline Development, G: Acute kidney injury: summary of NICE guidance. *BMJ*, 347: f4930, 2013.
7. Stevens, PE, Tamimi, NA, Al-Hasani, MK, Mikhail, AI, Kearney, E, Lapworth, R, Prosser, DI, Carmichael, P: Non-specialist management of acute renal failure. *QJM*, 94: 533-540, 2001.
8. NCEPOD: Acute Kidney Injury: Adding Insult to Injury. National Confidential Enquiry into Patient Outcomes and Death, 2009.
9. Aitken, E, Carruthers, C, Gall, L, Kerr, L, Geddes, C, Kingsmore, D: Acute kidney injury: outcomes and quality of care. *QJM*, 106: 323-332, 2013.
10. James, MT, Wald, R, Bell, CM, Tonelli, M, Hemmelgarn, BR, Waikar, SS, Chertow, GM: Weekend hospital admission, acute kidney injury, and mortality. *J Am Soc Nephrol*, 21: 845-851, 2010.
11. Wilson, FP, Shashaty, M, Testani, J, Aqeel, I, Borovskiy, Y, Ellenberg, SS, Feldman, HI, Fernandez, H, Gitelman, Y, Lin, J, Negoianu, D, Parikh, CR, Reese, PP, Urbani, R, Fuchs, B: Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. *Lancet*, 2015.
12. Ebah, L, Hanumapura, P, Waring, D, Challiner, R, Hayden, K, Alexander, J, Henney, R, Royston, R, Butterworth, C, Vincent, M, Heatley, S, Terriere, G, Pearson, R, Hutchison, A: A Multifaceted Quality Improvement Programme to Improve Acute Kidney Injury Care and Outcomes in a Large Teaching Hospital. *BMJ Qual Improv Rep*, 6, 2017.
13. Chandrasekar, T, Sharma, A, Tennent, L, Wong, C, Chamberlain, P, Abraham, KA: A Whole System Approach to Improving Mortality associated with Acute Kidney Injury. *QJM*, 2017.
14. Kolhe, NV, Reilly, T, Leung, J, Fluck, RJ, Swinscoe, KE, Selby, NM, Taal, MW: A simple care bundle for use in acute kidney injury: a propensity score matched cohort study. *Nephrology Dialysis Transplantation*, 2016.
15. Al-Jaghbeer, M, Dealmeida, D, Bilderback, A, Ambrosino, R, Kellum, JA: Clinical Decision Support for In-Hospital AKI. *J Am Soc Nephrol*, 29: 654-660, 2018.
16. Selby, NM, Casula, A, Lamming, L, Mohammed, M, Caskey, F, Tackling, AKII: Design and Rationale of 'Tackling Acute Kidney Injury', a Multicentre Quality Improvement Study. *Nephron*, 2016.
17. Campbell, MK, Piaggio, G, Elbourne, DR, Altman, DG, Group, C: Consort 2010 statement: extension to cluster randomised trials. *BMJ*, 345: e5661, 2012.
18. Hemming, K, Haines, TP, Chilton, PJ, Girling, AJ, Lilford, RJ: The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ*, 350: h391, 2015.
19. NHS England: Kidney Quality Improvement Partnership National Projects: Tackling AKI.
20. Selby, NM, Hill, R, Fluck, RJ: Standardizing the Early Identification of AKI: The NHS England National Patient Safety Alert. *Nephron*, 131: 113-117, 2015.
21. NHS England: Acute Kidney Injury (AKI) Programme, [www.thinkkidneys.nhs.uk](http://www.thinkkidneys.nhs.uk). 2014.

22. Resar, R, Griffin, FA, Haradan, C, Nolan, TW: Using Care Bundles to Improve Health Care Quality. IHI Innovation Series White Paper. Cambridge, Massachusetts, Institute for Healthcare Improvement. 2012.
23. KDIGO AKI Work Group: Section 2: AKI Definition. *Kidney inter, Suppl*, 2: 19-36, 2012.
24. Charlson, ME, Pompei, P, Ales, KL, MacKenzie, CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*, 40: 373-383, 1987.
25. Hemming, K, Girling, A: A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. *Stata Journal*, 14: 363-380, 2014.
26. Xu, X, Nie, S, Liu, Z, Chen, C, Xu, G, Zha, Y, Qian, J, Liu, B, Han, S, Xu, A, Xu, X, Hou, FF: Epidemiology and Clinical Correlates of AKI in Chinese Hospitalized Adults. *Clin J Am Soc Nephrol*, 10: 1510-1518, 2015.
27. Selby, NM, Crowley, L, Fluck, RJ, McIntyre, CW, Monaghan, J, Lawson, N, Kolhe, NV: Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. *Clin J Am Soc Nephrol*, 7: 533-540, 2012.
28. Olsen, CS, Clark, AE, Thomas, AM, Cook, LJ: Comparing least-squares and quantile regression approaches to analyzing median hospital charges. *Acad Emerg Med*, 19: 866-875, 2012.
29. Wei, Y, Carroll, RJ: Quantile Regression With Measurement Error. *J Am Stat Assoc*, 104: 1129-1143, 2009.
30. Susantitaphong, P, Cruz, DN, Cerda, J, Abulfaraj, M, Alqahtani, F, Koulouridis, I, Jaber, BL, Acute Kidney Injury Advisory Group of the American Society of, N: World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol*, 8: 1482-1493, 2013.
31. Coca, SG, Yusuf, B, Shlipak, MG, Garg, AX, Parikh, CR: Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*, 53: 961-973, 2009.
32. Mehta, RL, Cerda, J, Burdmann, EA, Tonelli, M, Garcia-Garcia, G, Jha, V, Susantitaphong, P, Rocco, M, Vanholder, R, Sever, MS, Cruz, D, Jaber, B, Lameire, NH, Lombardi, R, Lewington, A, Feehally, J, Finkelstein, F, Levin, N, Pannu, N, Thomas, B, Aronoff-Spencer, E, Remuzzi, G: International Society of Nephrology's Oby25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet*, 385: 2616-2643, 2015.
33. Holmes, J, Rainer, T, Geen, J, Roberts, G, May, K, Wilson, N, Williams, JD, Phillips, AO, Welsh, AKISG: Acute Kidney Injury in the Era of the AKI E-Alert. *Clin J Am Soc Nephrol*, 11: 2123-2131, 2016.
34. Phillips, D, Young, O, Holmes, J, Allen, LA, Roberts, G, Geen, J, Williams, JD, Phillips, AO, Welsh, AKISG: Seasonal pattern of incidence and outcome of Acute Kidney Injury: A national study of Welsh AKI electronic alerts. *Int J Clin Pract*, 71, 2017.
35. Selby, NM, Kolhe, NV, McIntyre, CW, Monaghan, J, Lawson, N, Elliott, D, Packington, R, Fluck, RJ: Defining the cause of death in hospitalised patients with acute kidney injury. *PLoS One*, 7: e48580, 2012.
36. Kerr, M, Bedford, M, Matthews, B, O'Donoghue, D: The economic impact of acute kidney injury in England. *Nephrol Dial Transplant*, 29: 1362-1368, 2014.
37. Palomba, H, Castro, I, Yu, L, Burdmann, EA: The duration of acute kidney injury after cardiac surgery increases the risk of long-term chronic kidney disease. *J Nephrol*, 30: 567-572, 2017.
38. Coca, SG, King, JT, Jr., Rosenthal, RA, Perkal, MF, Parikh, CR: The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. *Kidney Int*, 78: 926-933, 2010.
39. Sawhney, S, Marks, A, Ali, T, Clark, L, Fluck, N, Prescott, GJ, Simpson, WG, Black, C: Maximising Acute Kidney Injury Alerts - A Cross-Sectional Comparison with the Clinical Diagnosis. *PLoS One*, 10: e0131909, 2015.

## Tables and Figures

### Figure 1

Schematic of the stepped-wedge study design. After a six-month period of baseline data collection, the intervention (hospital wide AKI e-alert, care bundle and education programme) was sequentially introduced to participating sites across fixed three-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 three-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 three-month period of exposure to the intervention following 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; 5. Leeds St. James'.

### Figure 2

Change in hospital LoS (in days) comparing the effect of the intervention against control period. 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, gender, comorbid conditions, cluster (hospital) and seasonality, 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).

### Figure 3

Change in AKI duration (in days) comparing the effect of the intervention against control period. 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, gender, comorbid conditions, cluster (hospital) and seasonality, and the shaded area represents 95% CI. Results show a reduced AKI duration during in intervention period (from quantiles 0.8 onwards, effect size and median AKI duration at individual quantiles shown in the table).

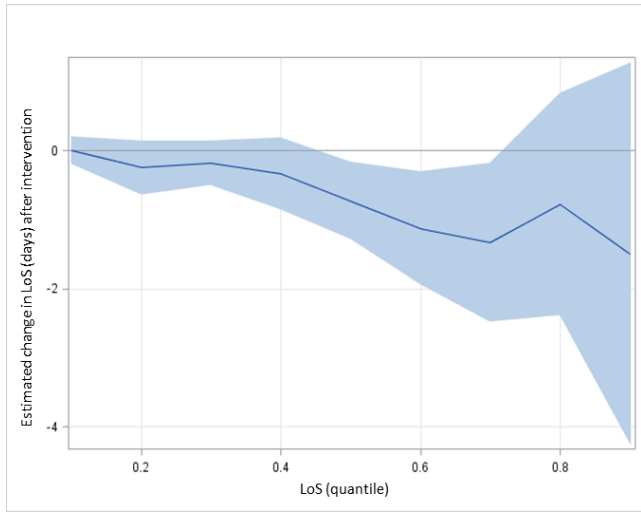
### Figure 4

Change in measures of AKI care comparing control and intervention periods. Urinary catheterisation was included as a balancing measure, and we did not observe an unintended

increase in the proportion of patients catheterised for reasons other than relief of urinary obstruction.

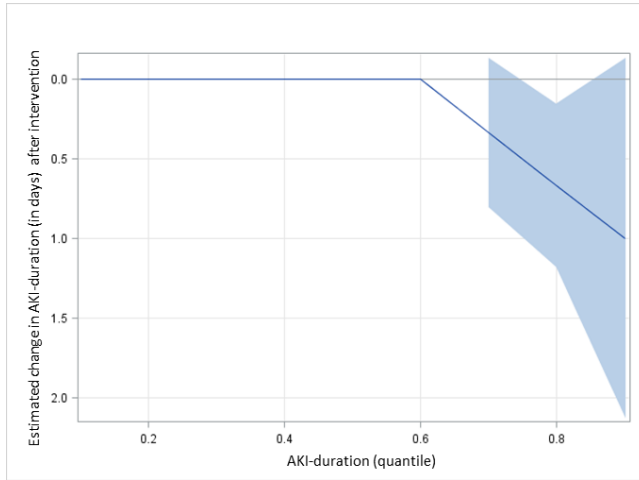
	Dec 2014- Feb 2015	March- May 2015	June-Aug 2015	Sept-Nov 2015	Dec 2015- Feb 2016	March- May 2016	June-Aug 2016	Sept-Nov 2016	Dec 2016- Feb 2017
Centre 1	Baseline data collection (pre- intervention)		Intervention <i>(transition period)</i>						
Centre 2				Intervention <i>(transition period)</i>					
Centre 3					Intervention <i>(transition period)</i>				
Centre 4						Intervention <i>(transition period)</i>			
Centre 5							Intervention <i>(transition period)</i>		

Figure 1



Quantile	Change in LoS (95% CI)	p-value	LoS at quantile (in days)	
			control	intervention
0.1	0 (-0.2 - 0.2)	1	2	2
0.2	-0.3 (-0.6 - 0.1)	0.3	4	3
0.3	-0.2 (-0.5 - 0.1)	0.5	6	5
0.4	-0.3 (-0.9 - 0.2)	0.08	8	7
0.5	-0.7 (-1.3 - -0.2)	0.04	10	8
0.6	-1.1 (-1.9 - -0.3)	0.03	13	11
0.7	-1.3 (-2.5 - -0.2)	0.03	17	15
0.8	-0.8 (-2.4 - 0.8)	0.7	24	21
0.9	-1.5 (-4.3 - 1.3)	0.2	36	31

Figure 2



Quantile	Change in AKI-duration (95% CI)	p-value	AKI-duration at quantile (in days)
0.2	0	1	1
0.4	0	1	1
0.6	0	1	2
0.7	-0.33 (-0.80 - 0.13)	0.16	3
0.8	-0.67 (-1.18 - -0.15)	0.01	5
0.9	-1.0 (-2.1 - 0.13)	0.08	9

Figure 3



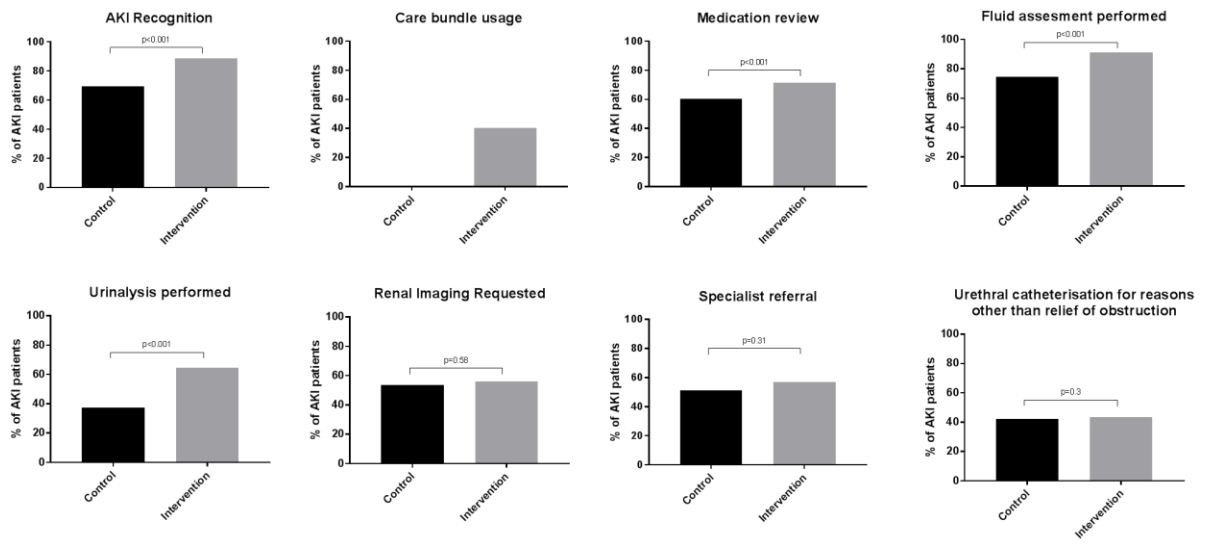


Figure 4

<b>Core elements of AKI care bundle common across all sites</b>
<b>Assess volume status and optimise blood pressure</b>
<b>Treat sepsis</b>
<b>Review medications and stop those contributing to AKI</b>
<b>Perform urinalysis</b>
<b>Referral (to nephrology or critical care outreach) for AKI stage 3, AKI with complications</b>

**Table 1A.**

Core elements that were included in care bundles at each of the Tacking AKI study sites. Sites were permitted to tailor the appearance of care bundles, and some sites included additional elements e.g. additional investigations into cause of AKI, manage hyperkalaemia, informing patient of presence of AKI.

<b>Type of education session</b>	<b>Number of sessions per centre</b>	<b>Target audience</b>	<b>Audience size</b>	<b>Duration</b>
<b>Launch event</b>	1	All members of staff welcome. Hospital chief executive, medical director, chief nurse attended	30-50	1 hour
<b>Hospital grand rounds *</b>	2	All grades of physicians, doctors in training and open to other specialties who wish to attend	40-80	1 hour
<b>Departmental educational or clinical governance meetings</b>	3-8	Departmental teaching to a range of specialties (e.g. emergency medicine, acute medicine, surgery, urology, rheumatology, elderly care)	10-20	1 hour
<b>Postgraduate teaching for doctors in training *</b>	3 per year (one for each grade of doctor)	AKI teaching as part of curriculum (essential teaching) for doctors in training, attendance often mandatory	20-40	1-2 hours
<b>Induction teaching for new staff *</b>	1-3	Shorter sessions, more focused on process rather than education per se	20-40	15mins
<b>Nursing, pharmacy and advanced practitioner teaching</b>	2-3	Varied between centres, from small group teaching to formal AKI study days for large groups	5-70	1 hour- whole day
<b>Ward based teaching sessions</b>	5-10	Formal teaching sessions at ward level	1-10	5-30 min
<b>Ad hoc teaching sessions</b>	20+	Informal teaching delivered by various members of the AKI team, included reminders of resources, case-based teaching	1-3	Varied, usually only minutes
<b>Other activities:</b>				
<ul style="list-style-type: none"> <li>• Publicity activities</li> <li>• E-learning, use of online teaching videos</li> </ul>				

**Table 1B**

Description of educational programme activities that were delivered across sites.

\* signifies activities that were already in place prior to the study.

	<b>Control</b>	<b>Intervention</b>
<b>Number of AKI episodes</b>	14,042	10,017
<b>% male</b>	50.3%	48.1%
<b>Age-group (%)</b>		
<b>18-59</b>	23.1%	20.3%
<b>60-69</b>	15.7%	15.3%
<b>70-79</b>	23.7%	23.5%
<b>80-89</b>	27.2%	29.8%
<b>90+</b>	10.3%	11.1%
<b>Median age (years)</b>	75.4	76.6
<b>Charlson co-morbidity score</b>		
<b>0</b>	16.4%	18.8%
<b>1</b>	20.3%	21.0%
<b>2</b>	20.2%	19.4%
<b>3+</b>	43.1%	40.8%
<b>Individual co-morbidities</b>		
<b>Previous myocardial infarction</b>	15.1%	14.4%
<b>Heart failure</b>	23.0%	22.6%
<b>Previous stroke</b>	7.0%	6.9%
<b>Diabetes mellitus</b>	27.3%	28.1%
<b>Chronic kidney disease</b>	22.0%	23.5%
<b>Chronic liver disease</b>	8.8%	7.0%
<b>Ethnicity</b>		
<b>Afro-Caribbean</b>	1.4%	0.8%
<b>South-Asian</b>	5.5%	5.9%
<b>Other</b>	2.8%	2.8%
<b>White</b>	86.1%	85.3%
<b>Missing</b>	4.2%	5.2%
<b>Social deprivation score* (%)</b>		
<b>1 (least deprived)</b>	23.6%	36.4%
<b>2</b>	17.8%	16.7%
<b>3</b>	16.0%	15.8%
<b>4</b>	15.7%	13.3%
<b>5 (most deprived)</b>	26.8%	17.6%
<b>Missing</b>	0.1%	0.2%
<b>Peak AKI stage (% per stage)</b>		
<b>1</b>	60.6%	64.5%
<b>2</b>	21.4%	19.8%
<b>3</b>	18.0%	15.7%
<b>Hospital-acquired AKI** (%)</b>	53.8%	49.4%

**Table 2**

Patient demographics in control and intervention periods. Please note that 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 randomised trial design. There were no major differences between control and intervention periods (including in AKI

severity) when patient demographics were analysed at a hospital level; these data are available in Supplementary Material.

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.

\* Social deprivation scores show the proportion of patients in each quintile of the Index of Multiple Deprivation.

\*\* Hospital acquired AKI defined as AKI onset >24 hours after hospital admission.

<b>Multilevel logistic regression for mortality</b>				
	<b>Odds ratio</b>	<b>95% CI</b>		<b>p-value</b>
<b>Intervention (reference=control period)</b>	1.04	0.91	1.21	0.55
<b>Time (linear trend)</b>	1.00	0.91	1.10	0.97
<b>Season (reference=spring)</b>				
<b>summer</b>	0.88	0.79	0.98	0.02
<b>autumn</b>	1.03	0.91	1.17	0.61
<b>winter</b>	1.13	1.04	1.22	0.005
<b>Age-group (reference=80+)</b>				
<b>18-34</b>	0.15	0.11	0.20	<0.0001
<b>35-49</b>	0.30	0.25	0.36	<0.0001
<b>50-64</b>	0.36	0.32	0.40	<0.0001
<b>65-79</b>	0.56	0.52	0.60	<0.0001
<b>Sex (reference=male)</b>	0.86	0.80	0.92	<0.0001
<b>Charlson comorbidity score (reference=0)</b>				
<b>1</b>	1.82	1.58	2.09	<0.0001
<b>2</b>	2.18	1.90	2.50	<0.0001
<b>3</b>	2.80	2.43	3.22	<0.0001
<b>4</b>	3.56	3.06	4.13	<0.0001
<b>5+</b>	5.76	5.03	6.59	<0.0001
<b>Hospital acquired AKI (reference community acquired)</b>	0.94	0.88	1.0	0.06

**Table 3**

Results of multilevel logistic regression for mortality. The period in which the hospitals were exposed to the intervention as compared with the control (reference) period is shown in the first row. Effects are seen with season, age, gender and co-morbidity, but there is no time-effect on mortality over the study period. Cluster (hospital) was also included in the model.

<b>Multilevel logistic regression for AKI progression</b>				
	<b>Odds ratio</b>	<b>95% CI</b>		<b>P-value</b>
<b>Intervention (reference=control period)</b>	0.94	0.80	1.10	0.41
<b>Time (linear trend)</b>	1.00	0.90	1.11	0.99
<b>Season (reference=spring)</b>				
<b>summer</b>	0.99	0.89	1.10	0.86
<b>autumn</b>	1.00	0.87	1.14	0.95
<b>winter</b>	1.03	0.94	1.13	0.58
<b>Age-group (reference=80+)</b>				
<b>18-34</b>	0.93	0.76	1.13	0.45
<b>35-49</b>	1.27	1.08	1.48	0.003
<b>50-64</b>	1.20	1.08	1.34	0.001
<b>65-79</b>	1.19	1.09	1.30	<0.0001
<b>Sex (reference=Male)</b>	0.83	0.77	0.90	<0.0001
<b>Charlson comorbidity score (reference=0)</b>				
<b>1</b>	1.18	1.03	1.36	0.018
<b>2</b>	1.58	1.38	1.81	<0.0001
<b>3</b>	1.85	1.60	2.14	<0.0001
<b>4</b>	2.30	1.98	2.68	<0.0001
<b>5+</b>	2.32	2.03	2.66	<0.0001
<b>Hospital acquired AKI (reference community acquired)</b>	0.96	0.89	1.03	0.26

**Table 4**

Results of multilevel logistic regression for AKI progression. AKI progression was defined as AKI stage 1 or 2 that worsened to a higher stage of AKI. The period in which the hospitals were exposed to the intervention as compared with the control (reference) period is shown in the first row. Cluster (hospital) was also included in the model.