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

List of collaborators

Nick Selby

Fergus Caskey

Anna Casula

Erik Lenguerrand

Shona Methven

Margaret May

Table of contents:

List of abbreviation:

AKI	Acute kidney injury
AT	As treated
CKD	Chronic kidney disease
CRT	Cluster randomised trial
HSCIC	Health and social care information centre
ICC	Intra-cluster correlation
ICU	Intensive care unit
ITT	Intention to treat
PAS	Patient administration systems
PP	Per protocol
RCT	Randomised control trial
RRT	Renal replacement therapy
SAP	Statistical analysis plan
SWCRT	Stepped-wedge cluster randomised trial
UKRR	United Kingdom Renal Registry

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 at 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.

Block	Dec'14-Feb'15	Mar-May'15	Jun-Aug'15	Sep-Nov'15	Dec'15-Feb'16	Mar-May'16	Jun-Aug'16	Sep-Nov'16
A	0	0	**T**	1	1	1	1	1
B	0	0	1	**T**	1	1	1	1
C	0	0	1	1	**T**	1	1	1
D	0	0	1	1	1	**T**	1	1
E	0	0	1	1	1	1	**T**	1

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 30days of first AKI warning stage result 0=survived to >30days)
- 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 (>=18yrs 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

Hospital		N total overnight Hospitalisations	N episodes of AKI (N patients)	N hospitalisation with AKI and complete covariates (% of tot AKI)
A	TP_1	20,000	500 (450)	480 (96%)
	TP_2			
	TP_3			
	TP_4			
	TP_5			
	TP_6			
	TP_7	21000	580 (540)	550 (95%)
	TP_8		etc.	
B	TP-1	16,000		
	TP-2	15,500		
	TP-3	16,500		
	TP-4			
	TP-5			
	etc.			

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-3

Hospital	Variable	Control	Exposed
A	N episodes (N patients) % male Ethnicity age-group comorbidity score % AKI levels (1-2-3) % h-AKI over total AKI (or incidence of h- AKI) N deaths by 30days Length hosp-stay (median-IQR) N Critical care (% >0) N recovered (%) N progressed (%)		
B etc	N % male Ethnicity age-group		

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.

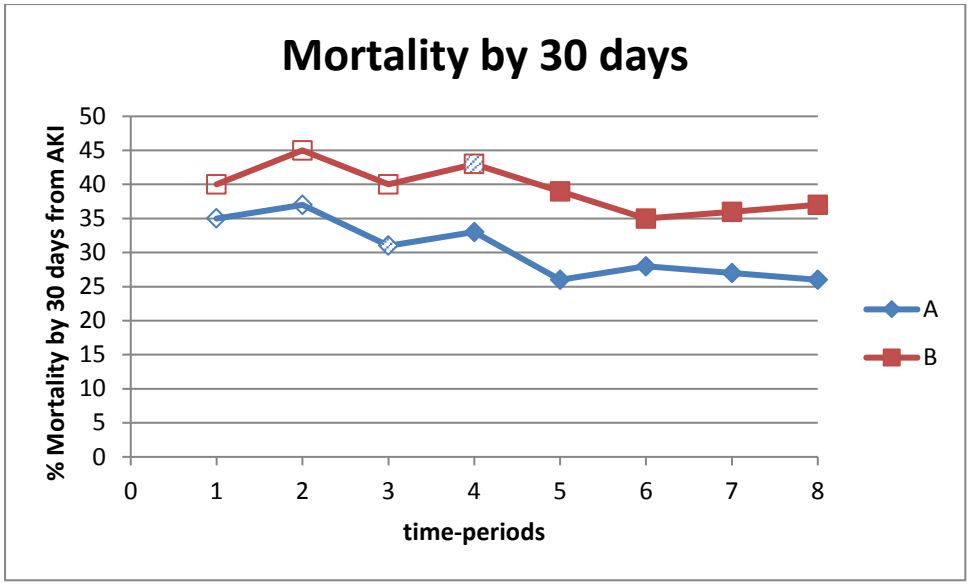

Figure-1. Example of graphical presentation of 30-days mortality data for hospitals A and B, where empty symbol=control, pattern symbol=transition, full symbol=exposed).

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 at 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

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 (T_{ij}), equals 1 if intervention present at cluster I at time J, else it is 0.
- A fixed treatment effect (θ)
- Fixed time effect (γ_j) (one parameter if calendar time used as continuous variable, otherwise vector)
- Fixed effects [β] for patient-level demographics
- Patient-level adjustment variables [X_k]
- Random cluster effect (α_i)
- Residual noise (ε_{ijk})

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

MODEL-1 $\text{Logit}(Y_{ik}) = \theta * T_i + \alpha_i + \varepsilon_{ik}$

Where Y_{ik} = probability of the episode to have response=1 (death by 30-days after AKI)
θ = log 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 $\text{Logit}(Y_{ijk}) = \theta * T_{ij} + \gamma_j + \alpha_i + \varepsilon_{ijk}$

Where γ= 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 $\text{Logit}(Y_{ijk}) = \theta * T_{ij} + \gamma_j + [\beta]X_{ijk} + \alpha_i + \varepsilon_{ijk}$

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

Where ω = 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

Block	Dec'14-Feb'15	Mar-May'15	Jun-Aug'15	Sep-Nov'15	Dec'15-Feb'16	Mar-May'16	Jun-Aug'16	Sep-Nov'16
A-protocol	0	0	**T**	1	1	1	1	1
A-as done	0	0	0	0	**T**	1	1	1
A-data used	YES	YES	**NO**	**NO**	**NO**	YES	YES	YES

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 $\text{Log}(Y_{ij}) = \log(\text{exposure}_{ij}) + \theta * T_{ij} + \gamma_j + \alpha_i$

Where Yij = count of AKI episodes in hospital I 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

	Dec 2014 - Nov 2015				Dec 2015 - Nov 2016				Dec 2016 - Nov 2017			
	D-F	M_M	J-A	S-N	D-F	M_M	J-A	S-N	D-F	M_M	J-A	S-N
Develop statistical analysis plan												
Randomise units to steps												
Baseline period-1												
Baseline period-2												
1st Transition												
2nd Transition												
3rd Transition												
4th Transition												
5th Transition												
Last period, all on treatment												
Provide 1st report on data												
Statistical analysis and write up												

REFERENCES

Balasubramanian, G., et al., *Early nephrologist involvement in hospital-acquired acute kidney injury: a pilot study.* Am J Kidney Dis, 2011. 57(2): p. 228-34.

Campbell MK, Piaggio G, Elbourne DR, Altman DG; CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012 Sep 4;345:e5661.

Chawla, L.S., et al., *Acute kidney injury and chronic kidney disease as interconnected syndromes.* N Engl J Med, 2014. 371(1): p. 58-66.

Hemming and Girling, The Stata Journal, 2014, Vol 14, N 2: pp. 363-380

Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015 Feb 6;350:h391.

Hussey MA and Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials. 2007 Feb;28(2):182-91.

Kerr, M., et al., *The economic impact of acute kidney injury in England.* Nephrol Dial Transplant, 2014. 29(7): p. 1362-8.

NCEPOD, *Acute Kidney Injury: Adding Insult to Injury*. 2009, National Confidential Enquiry into Patient Outcomes and Death

Selby, N.M., et al., *Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients.* Clin J Am Soc Nephrol, 2012. 7(4): p. 533-40.

Wang, H.E., et al., *Acute Kidney Injury and Mortality in Hospitalized Patients.* Am J Nephrol, 2012. 35(4): p. 349-355.