Renal Replacement Anticoagulant Management (RRAM)

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Role, Name and Position	**Signature**	**Date**
Chief Investigator: Dr Peter Watkinson (Associate Professor, University of Oxford)		
Sponsor: Ms Kerrie Gemmill (Intensive Care National Audit & Research Centre)		

Contents

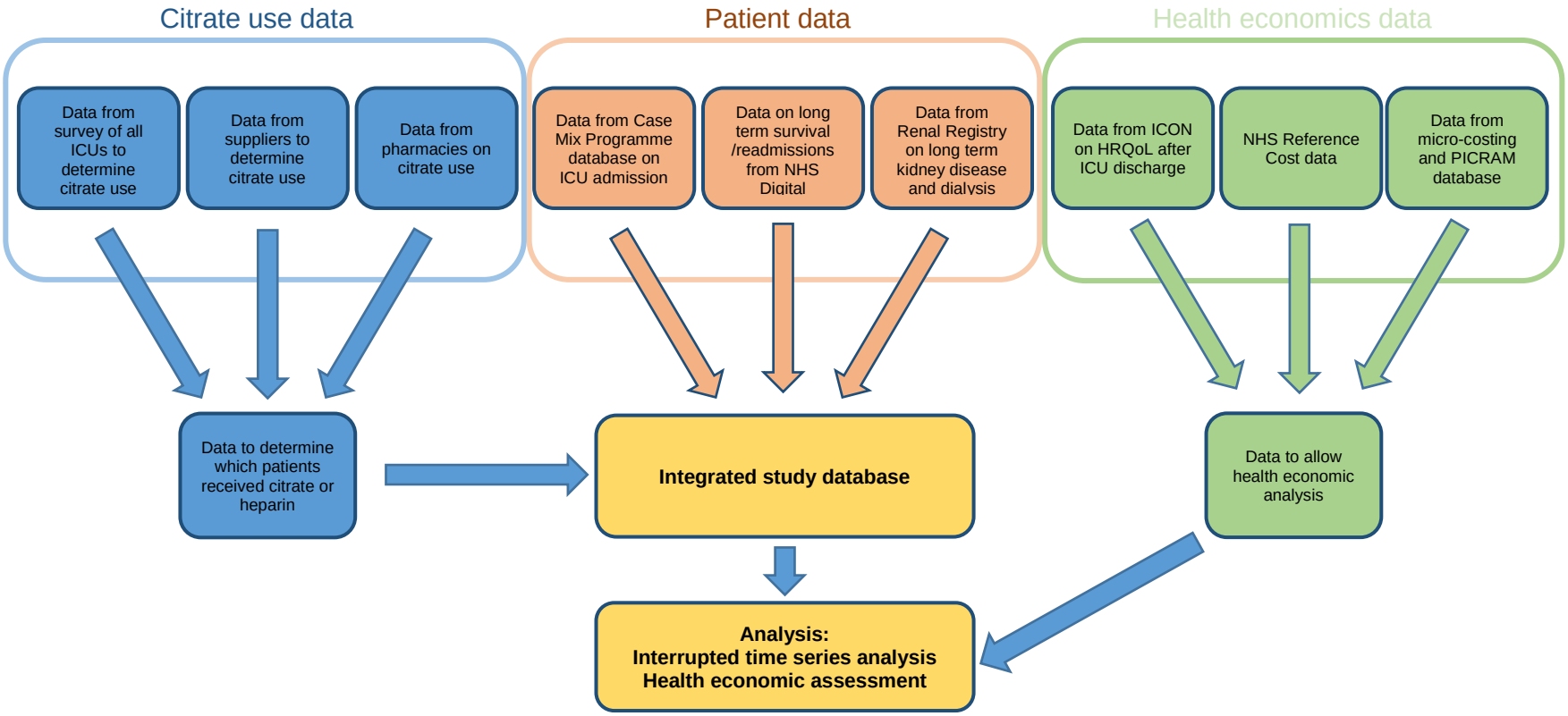
Abbreviations

CAG	Confidentiality Advisory Group
CCMDS	Critical Care Minimum Dataset
CEA	Cost-effectiveness Analysis
CMP	Case Mix Programme
CRRT	Continuous Renal Replacement Therapy
DARS	Data Access Request Service (NHS Digital)
ESRD	End-Stage Renal Disease
HES	Hospital Episode Statistics
HICF	Health Information Challenge Fund
HRQoL	Health-Related Quality of Life
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th revision)
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
INB	Incremental Net monetary Benefits
ITS	Interrupted Time Series
IRAS	Integrated Research Application System
MICE	Multivariate Imputation by Chained Equations
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ONS	Office for National Statistics
QALY	Quality-Adjusted Life Year
RCA	Regional Citrate Anticoagulation
REC	Research Ethics Committee
RRAM	Renal Replacement Anticoagulation Management
SHA	Systemic Heparin Anticoagulation
UKRR	UK Renal Registry

1 Trial summary

Title:	Renal Replacement Anticoagulant Management
Short Title/acronym:	RRAM
Sponsor name:	Intensive Care National Audit & Research Centre (ICNARC)
Funder name & reference:	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, 16/111/136
Design:	Observational comparative effectiveness study of individual patient data using interrupted time series analysis techniques of linked data sources
Aim:	To establish clinical and health economic effects of moving from systemic heparin anticoagulation to regional citrate anticoagulation during continuous renal replacement therapy (CRRT) for patients treated on non-specialist Intensive Care Units (ICUs) in England and Wales
Primary outcomes:	Primary clinical effectiveness outcome: • All-cause mortality at 90 days Primary health economic outcome: • Incremental net monetary benefit at one year
Secondary outcomes:	Secondary clinical effectiveness outcomes: • All-cause mortality at hospital discharge, 30 days and one year • Days of renal, cardiovascular, and advanced respiratory support • ICU and hospital length of stay • New dialysis-dependent renal disease at one year Secondary health economic outcomes: • Estimated lifetime incremental net benefit
Inclusion criteria:	• Age 16 years or greater • Admitted to an ICU participating in the ICNARC Case Mix Programme (CMP) in England between 1 April 2009 and 31st March 2017
Exclusion criteria:	• Pre-existing end-stage renal disease (ESRD) • Admitted to an ICU after kidney or kidney-pancreas transplantation • Primary admission with acute hepatic failure
Setting:	184 non-specialist adult ICUs in England or Wales
Anticipated sample size:	85,000 adult critical care patients
Anticipated study duration:	15 months

2 Study flow diagram



3 Background and rationale

About one in five critically ill patients develop an acute kidney injury (AKI, previously called acute renal failure). (1) Over half these patients require renal replacement therapy to prevent harm from electrolyte disturbance, fluid overload and uraemia. Although some countries still use intermittent haemodialysis for acute renal replacement therapy, continuous renal replacement therapy (CRRT) is used for renal replacement in 95% of UK ICUs. (2) The machines used for CRRT are similar to dialysis machines. They pump a patient's blood through a polyvinyl chloride extracorporeal circuit and a polysulphone/polycarbonate haemodiafilter cartridge. The plastic circuit and cartridge activate clotting factors in the circulating blood, therefore if coagulation is not controlled the cartridge or circuit will be rapidly blocked by blood clots. Traditionally heparin is added to the blood as it enters the circuit to prevent coagulation (systemic heparin anticoagulation or SHA) to prevent this from occurring. However, the machine does not remove much of the heparin, and most returns to the patient in their blood. This reduces the ability of the patient's blood to clot, increasing their risk of bleeding, which is particularly dangerous for critically ill patients, who already have a high risk of bleeding.

Regional citrate anticoagulation (RCA) is an alternative to using heparin. RCA prevents blood clotting by chelating ionised calcium (which is needed for the blood to clot) using a citrate solution added to the patient's blood as it enters the CRRT machine. The effect of the citrate is reversed by infusing calcium chloride or calcium gluconate solution into the patient's blood as it is returned to their circulation, thus restoring its ability to clot and reducing the risk of bleeding. However, there are other risks with citrate anticoagulation. Citrate can cause changes in the amount of calcium in circulating blood, and alters the blood acid-alkali balance. These in turn can cause problems with muscle weakness, heart function, bone health, and breathing. As a result, overall anticoagulation using citrate could be better or worse than heparin for patients.

Currently, citrate-based anticoagulation is rapidly replacing heparin-based anticoagulation during CRRT in ICUs in the UK. We undertook a preliminary survey of 76 ICUs conducted through the United Kingdom Clinical Pharmacy Association (UKCPA) critical care pharmacist network to inform this application. When surveyed 39 (51%) had already changed from heparin to citrate, and 3 (4%) were in the process of changing. However, this rapid adoption is occurring without any large studies showing citrate to be cheaper, more effective or even equivalently safe as heparin.

4 Aims and objectives

4.1 Aim

The aim of the RRAM study is to establish the clinical and health economic effects of moving from SHA to RCA during CRRT for patients treated on non-specialist ICUs in England and Wales.

4.2 Objectives

1. Investigate the short-term benefits, risks, and costs of citrate anticoagulation.

2. Provide information on the subsequent development of end-stage renal disease (ESRD).

3. Trial the efficient research techniques, that if successful could be used to track the effects of any change in critical care practice occurring in ICUs in England and Wales over a reasonably short time scale.

5 Study design and conduct

Observational comparative effectiveness study of individual patient data using interrupted time series analysis techniques of linked data sources.

5.1 Efficient design

Most of the data for the RRAM study will come from record-linkage using data already collected from the Intensive Care National Audit & Research Centre (ICNARC) Case Mix protocol (CMP), NHS Digital and UK Renal Registry (UKRR), and is therefore an efficient study-design making use of available high-quality data to assess the clinical and cost effectiveness for the NHS of the change from SHA to RCA.

5.2 Sampling

The selection of sites is based on those taking part in the ICNARC Case Mix Programme (CMP). The CMP is a comparative national clinical audit involving nearly all UK ICUs in England and Wales. We will link data for the period 1st April 2009 and 31st March 2017 with the Renal Registry and HES/ONS databases through NHS Digital.

5.3 Setting

Adult, general ICUs (critical care units delivering Level 3 critical care, and excluding standalone high dependency units and specialist ICUs, for example, neurosurgical, cardiothoracic or liver ICUs) in England and Wales.

5.4 Population

Critically ill adults who received CRRT on one or more day whilst treated on an ICU

5.4.1 Inclusion criteria

- Age ≥16 years.
- Admitted to an adult, general ICU in England participating in the CMP between 1 April 2009 and 31 March 2017.
- Receipt of CRRT in ICU, identified by the recording of renal support, as defined by the Critical Care Minimum Dataset (CCMDS), on at least one calendar day during the ICU stay.

5.4.2 Exclusion Criteria

- Patients with pre-existing ESRD, identified by the recording of a requirement for chronic renal replacement therapy for ESRD in the CMP dataset.
- Patients admitted to an ICU after kidney or multi-organ including kidney transplantation
- Primary admission with acute hepatic failure.

5.5 Exposure

RCA for CRRT, identified by admission to ICU after the date on which the ICU indicates that they transitioned from SHA to RCA for CRRT. A suitable run-in period will be determined by analysis of consumable use to estimate average time for near-complete RCA adoption.

5.6 Comparator

SHA for CRRT, identified by admission to ICU before the date on which the ICU indicates that they transitioned from SHA to RCA for CRRT or admission to an ICU that has not transitioned to RCA.

5.7 Outcomes

5.7.1 Primary outcome – Clinical effectiveness:

- all-cause mortality 90 days after first ICU admission in which CRRT was received.

5.7.2 Primary outcome – Health economic:

- incremental net monetary benefit gained at one year at a willingness-to-pay of £20,000 per quality-adjusted life year (QALY) associated with a change from heparin to citrate anticoagulation during CRRT.

5.7.3 Secondary outcomes:

- all-cause mortality at hospital discharge, 30 days and one year after ICU admission
- days of renal, cardiovascular, and advanced respiratory support whilst in ICU
- ICU and hospital length of stay
- new dialysis-dependent (end-stage) renal disease at one year after ICU admission.
- estimated lifetime incremental net benefit associated with a change from heparin to citrate anticoagulation during CRRT.

5.8 Data sources for clinical outcomes

Mortality at hospital discharge, days of organ support, ICU and hospital length of stay will be obtained from the CMP database. The data collected include fields to determine whether a patient received CRRT, and the duration of CRRT whilst the patient was in an ICU (3).

Longer term survival, date of death after hospital discharge, and any subsequent hospital readmissions will be determined from data linkage through NHS Digital.

Patients who go on to develop dialysis-dependent renal disease will be identified through data linkage with the UKRR (http://www.renalreg.com/).

5.9 Data sources for health economic outcomes

5.9.1 Resource use associated with alternative interventions

Resource use associated with SHA and RCA, such as disposable and non-disposable equipment, drugs, fluids and staff costs, will be obtained using cognitive walk through techniques. CRRT system set-up time and frequency will be obtained from the PICRAM dataset (see section 6.3).

5.9.2 Length of stay and episodes of treatment received for renal disease

Days of treatment in an ICU, days of organ support and days on acute hospital wards during the index illness will be obtained from the CMP database. Subsequent days of hospitalisation, bleeding and thromboembolic episodes will be obtained by linkage with HES. Patients developing dialysis-dependent renal disease, requiring acute post-ICU haemodialysis or undergoing renal transplantation will be identified by linkage with UKRR.

5.9.3 Unit costs

Local unit costs for consumables will be obtained via members of the UK Clinical Pharmacy Association critical care pharmacist network. Unit costs of staff time will be obtained from national sources. Unit costs for acute hospital ward and ICU care, and dialysis sessions will be obtained from the NHS Reference Costs 2015-16.(4)

5.9.4 Health-related quality of life

Health-related quality of life (HRQoL), using the EuroQol (EQ-5D-3L) questionnaire, will be obtained from the ICON study database.

5.10 Data collection and management

The RRAM study plan consists of the following components, many of which will run in parallel.

5.10.1 UKCPA survey to obtain citrate vs. heparin usage data

We will survey the critical care pharmacist network to obtain data on which ICUs are using citrate anticoagulation for CRRT and the date they changed from heparin. In ICUs where there is no named critical care pharmacist, or where we cannot obtain a response, one of the research team will telephone the identified main contact person, held by ICNARC, for the CMP at that ICU to obtain the information. In the unlikely event we are still unable to obtain the information, one of the clinical team will contact the ICU Clinical Lead. Responses will be verified by comparing against the lists of ICUs using citrate anticoagulation supplied by the two UK suppliers of citrate based CRRT equipment. In addition to citrate usage we will also collect data on the type of machine and haemodiafiltration cartridge used for citrate-anticoagulated CRRT, which will also allow us to select which ICUs to approach for the micro-costing study.

5.10.2 Determining the extent of continuing heparin use in ICUs that have changed to citrate

We will then identify ICUs where the anticoagulation for CRRT changed from heparin to citrate. However, we will ensure that we only study ICUs where the change in anticoagulation was almost complete. We will ask for purchase details of CRRT consumables from all ICUs. As citrate uses different consumables, we will be able to estimate the relative use of citrate and heparin. Survey data will then be confirmed in a small number of ICUs with advanced IT systems where we will ask for details of anticoagulation from the ICU computerised information systems (CIS) and obtain consumable use. As consumable usage is also likely to differ between the CRRT machines from different suppliers, we will include ICUs using different machines to extract data from CIS. We expect sporadic use of heparin in all ICUs to treat specific patients, such as those with hepato-renal failure, but these patients will be excluded using fields recording acute hepatic failure in the CMP data prior to analysis.

5.10.3 Identification of patients who received CRRT in ICUs after they changed to citrate anticoagulation

Once a change-over date to citrate has been established for each ICU that has changed, and we have checked that no units are continuing to use both anticoagulants routinely, we will determine which patients received CRRT on one or more days from the appropriate fields in the CMP database. Patients who are recorded as having pre-existing ESRD or who are admitted to ICU following kidney or kidney-pancreas transplantation will be excluded. Patient groups expected continue to receive SHA (such as patients with hepatic failure) will also be excluded. We will need to allow a wash-in period for the change-over to citrate anticoagulation. We believe this will be short, but we will establish an appropriate period from data collected in the initial survey about change-over to citrate-based anticoagulation.

5.10.4 Identification of patients who received CRRT from ICUs that change to citrate prior to the change (i.e. received heparin)

We will go back from the date of change to citrate to 1 April 2009 and identify all patients who received CRRT on one or more days. The same exclusions (ESRD and transplantation) will apply.

5.10.5 Identification of a control group from patients who received CRRT from ICUs that have not changed to citrate anticoagulation

In all ICUs that have not changed to citrate we will identify all patients who received CRRT on one or more day back to 1 April 2009. Again, the same exclusions (ESRD and transplantation) will apply.

5.11 Data linkage

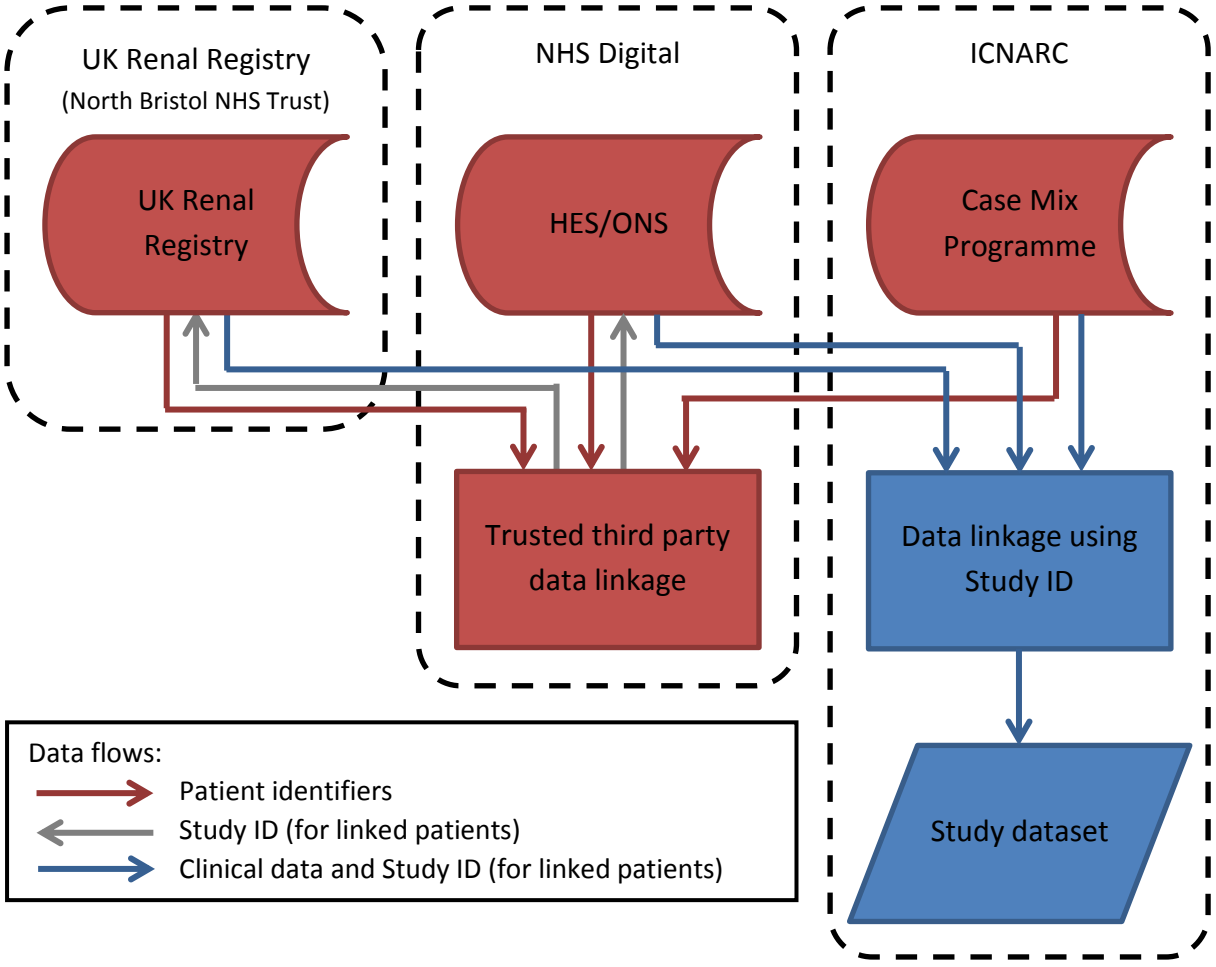
Data linkage will be undertaken by NHS Digital acting as a 'trusted third party' (see: figure 1). Identifiers (with no associated clinical data) will be uploaded from the CMP and UKRR clinical audits to secure servers at NHS Digital, who will perform the data linkage and return to each audit their local identifier (a field that is unique to the records within that dataset) together with a common key that will be used to link all records of the same patient across datasets. The UKRR will then transfer to ICNARC the

agreed pseudonymised dataset (including the common key) for successfully linked patients. Similarly, NHS Digital will perform a pseudonymised data extract of agreed fields from HES and ONS datasets and pass these to ICNARC (again including the common key for data linkage). ICNARC will then produce a pseudonymised data extract from the CMP that will be linked with extracts from the UKRR, HES, and ONS datasets using the common key. In this way, only pseudonymised data will be linked between the multiple data sources.

5.11.1 Data cleaning and validation

We will perform range and logical checks on the Renal Registry and HES/ONS data. ICNARC data has all undergone an extensive data cleaning and validation process including range checks, logical checks (date sequences etc.) and where needed checking against source data. We therefore do not expect any further cleaning/validation will be required before locking the database for analysis.

Figure 1. Study patient data flows



6 Statistics and data analysis

6.1.1 Power calculation

Based on CMP data we anticipate a total available sample size of approximately 85,000 patients from 184 ICUs. The UK suppliers indicate that 90 ICUs are currently using RCA. To assess the likely power of the available data to address the research question of interest, we simulated 1000 replications of the study using available CMP data under the following assumptions:

- 35 changes from SHA to RCA will be observed within the available data. This is a conservative assumption from the 90 ICUs across the UK reported to be using RCA, to allow for use in ICUs outside England, specialist ICUs and changes that occurred when ICUs were not participating in the CMP. In each simulation, 35 ICUs were selected at random to represent the observed changes.

- Changes from SHA to RCA will be evenly distributed over the time period of the study. In the simulations, the changeover quarter for each of the 35 randomly selected ICUs was sampled from a uniform distribution from between their second and penultimate quarters.

- 15 ICUs will have changed from SHA to RCA prior to the start of the study. In each the simulation, 15 ICUs were selected at random to contribute data to the RCA group throughout. In the simulations, the indicator t_{ij} is used to indicate ICU i was using RCA in quarter j.

- The distribution of risk of 90-day mortality for patients receiving renal replacement therapy in UK ICUs will follow that of the ICNARC$_{H\text{-}2015}$ model for acute hospital mortality in critical care. This model was developed in a recent NIHR-funded study, and has excellent discrimination (are under the receiver operating characteristic curve ~0.9) and calibration in this population. In the simulation, the patient level risk of death for patient k admitted in quarter j to ICU i, p_{ijk}, was calculated using this model.

- The between ICU standard deviation for 90-day mortality will be 0.22. This value was estimated as the observed value for risk-adjusted acute hospital mortality in the CMP among patients receiving renal replacement therapy and corresponds to an ICC of 0.015. In each simulation, an ICU-level effect for ICU i, u_i, was sampled from a Normal distribution with mean 0 and standard deviation 0.22. For the purpose of the simulations, no clustering of observations for patients within quarters in the same ICU was assumed.

- Changing from SHA to RCA will be associated with an odds ratio for 90-day mortality of 0.9. For the purpose of simulation, only a change in level was considered with no change in slope.

In each simulation, the 'observed' outcome for each patient, y_{ijk}, was sampled from a Bernoulli distribution based on the following model:

$$\text{logit}(y_{ijk}) \sim \text{logit}(p_{ijk}) + \ln(0.9) \times t_{ij} + u_i$$

The estimated treatment effect within each simulation was then estimated using a multilevel logistic regression with robust standard errors. Simulations were undertaken using Stata/SE version 14.2

(StataCorp LP, College Station, TX). The random number seed was set prior to analysis to ensure reproducibility of results.

The results of the simulations show this sample will have approximately 81% power (P<0.05) to detect a step change in 90-day mortality corresponding to an odds ratio of 0.9.

6.2 Clinical effectiveness analyses

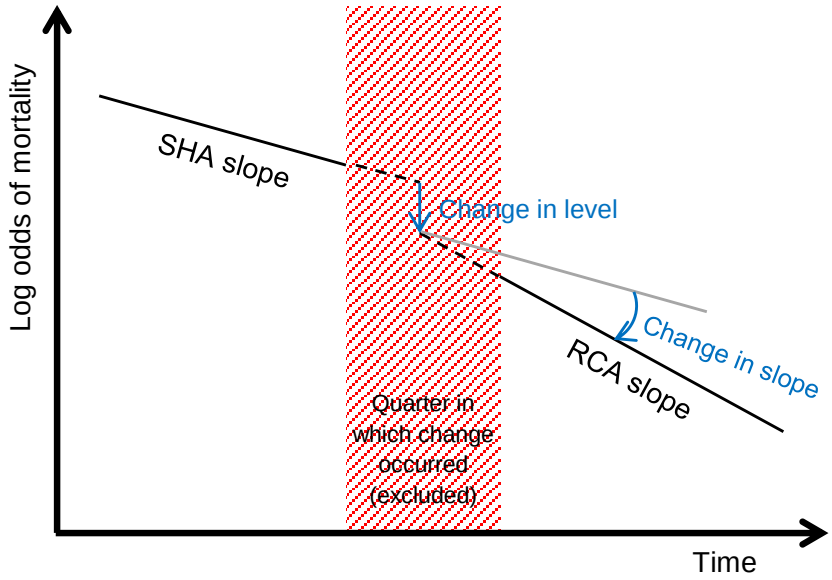
6.2.1 Approach to analysis

The analysis will follow interrupted time series (ITS) analysis techniques, where the interruption corresponds to the change from SHA to RCA for CRRT. This technique is considerably better than simple 'before and after' comparisons as it allows for statistical investigation of potential biases in the estimate of the effect of the intervention. These biases include secular trends, where the outcome may be changing over time, cyclical or seasonal trends, random fluctuation and autocorrelation. The study design will follow the eight quality criteria for ITS design and analysis described by Ramsay et al. (5) (for our assessment of our study against these quality criteria, see Appendix 1).

Random effects multilevel generalised linear models (logistic for binary outcomes and linear for continuous outcomes) will be used to estimate the ICU-specific effect of the intervention. The unit of analysis will be the individual patient, with patients nested within time periods (quarters) nested within ICUs. The study will include periods both before and after the switch from SHA to RCA in individual units and a comparator group of ICUs that did not change treatment. The effect estimate will be the within ICU change in trends with the control ICUs primarily improving estimates of patient-level confounders and underlying secular trend. Models will be fitted with robust standard errors to allow for model misspecification, including autocorrelation and heteroscedasticity. Doubly-robust approaches will be considered should concerns about model misclassification arise.

The primary impact model for the effect of the change from SHA to RCA will allow for both a change in level and in slope (Figure 2). Linear trends will be assumed in both the pre-intervention and post-intervention periods. The quarter of data in which the change from SHA to RCA took place will be omitted from the model to allow for potential imprecision in the reporting of the time of change and time to transition from one modality to the other. The need for, and duration of, any further 'wash-in' period will be established from data collected in the initial survey about change from SHA to RCA. The potential for lagged and temporary effects will be explored in sensitivity analyses. The regression models will be adjusted for patient case mix using risk prediction models for 90-day and one-year mortality being developed in an ongoing NIHR-funded project (HS&DR 14/19/06),(6) which builds on considerable previous work in risk modelling in this patient group.(7, 8) The unit of analysis at the individual patient level, rather than collapsing into a monthly or quarterly time series, has been selected to maximise the use of available high-quality individual patient data, which is strongly predictive of outcome. The results of the regression models will be reported as the odds ratio (or for continuous outcomes, difference in means) with 95% confidence interval for the change in level and the odds ratio per year (difference in means per year) with 95% confidence interval for the change in slope associated with the change from SHA to RCA. The overall significance of the change from SHA to RCA will be assessed by the joint test of the two parameters for the change in level and change in slope.

Figure 2. Primary impact model



6.2.2 Handling of missing data

Any ICUs for which it is not possible to establish whether/when a change from SHA to RCA for CRRT occurred will be excluded from the analysis. Missing values in individual patient covariates will be imputed using fully conditional specification implemented using the Multivariate Imputation by Chained Equations (MICE) algorithm.(9, 10) The multiple imputation model will include all covariates planned to be included in the substantive model, plus the intervention and outcome measures.(11) To ensure reproducibility of results, the random number seed will be set prior to producing the imputed datasets.

6.2.3 Management of confounders

Our study design is most susceptible to time-varying confounders. This is particularly an issue if the confounders change over the same period as the intervention. As the primary outcome is mortality, the confounders of interest are those that alter mortality over time. These confounders could be at the patient level, time trends or seasonal.

At a patient level, the mortality might change over time because of a change in case mix which in turn alters absolute mortality. However, it is unlikely there would be step changes in the case mix synchronous with a change in anticoagulation for CRRT. ICNARC has developed high quality risk-adjustment models to predict hospital mortality(8) and is developing new models for 90-day and one-year mortality.(6) These will form the basis for patient-level risk adjustment. Due to the potential that individual risk factors will have a different association with mortality when evaluated in the subpopulation of ICU admissions receiving CRRT, the risk adjustment will include all individual covariates from the risk adjustment models rather than the predicted log odds of mortality.

We already know that case mix adjusted hospital mortality for patients treated on ICUs in the UK and elsewhere is decreasing over time. Any change in absolute mortality will be corrected for as part of

the analysis by determining trends in mortality over the period before the change to citrate and factoring this into the analysis. The control ICUs will also be analysed to mitigate any unobserved time-varying confounders, again allowing for a correction if a trend is found.

Seasonality will be addressed by including indicators for the four seasons at the quarter level in the regression models.

6.3 Health economic analyses

6.3.1 Approach to analysis

The cost analysis will take a health services perspective. Resource use associated with the study interventions will be measured using a micro-costing method (see below). We will only cost the RCA after training for the change from SHA is complete; the cost of the changeover will not be estimated. Resource use associated with ICU and hospital stay, and episodes of related treatment will be costed using patient level data obtained from the linked CMP-HES-UKRR dataset. As resource use and costs are likely to differ between CRRT machines from different manufacturers, we will ensure that this is captured in the economic analyses by selecting ICUs supplied by different manufactures.

6.3.2 Measurement of costs

6.3.2.1 Micro-costing study

To retain the efficient study design we will undertake cognitive walk through (including hierarchical task analysis) with representative clinicians, rather than undertaking the more costly "structured observation" approach.(12) Here users mentally "walk through" the set-up and running of a CRRT device, allowing staff time and consumables for each task element to be estimated. The approach will allow us to gather information from more units and more representative staff cost-effectively, improving generalisability. We will involve representative staff from a minimum of five units. Interviews of providers will be supported by sensitivity analysis around the base case values. This approach has been successfully used by in previous NIHR-funded studies.(13, 14)

6.3.2.2 Set-up time

The system set-up time is expected to drive the difference in staff time between the two anticoagulation techniques, both because systems may differ in the time for initial set-up and because SHA and RCA may differ in the frequency with which the system fails.

A Health Information Challenge Fund (HICF)-funded study in Oxford has generated a highly-detailed, anonymised research database of all patients treated on both Oxford general ICUs and the Royal Berkshire Hospital ICU in Reading from 2009 onwards (PICRAM, HICF 0510 006). We can determine from these data the number and distribution of intervals between one CRRT system failing and the next being in place and running (recommissioning of CRRT) for hundreds of such events when both citrate and heparin are in use.

6.3.2.3 Long-term dialysis

Patients identified from UKRR as receiving dialysis will be assumed to be having three dialysis sessions per week from the date of first renal replacement recorded in the registry.

Patient-level resource use data will be combined with appropriate unit costs to report total costs per patient for up to one year since ICU admission.

6.3.2.4 Health-related quality of life and quality-adjusted life years

The study will use EQ-5D data from the 8000 patient ICON study which administered EQ-5D questionnaires at three months, one year and two years after ICU discharge.(15, 16) ICON is already cross-linked to CMP data, allowing selection of patients who received CRRT. We will divide these patients into quartiles of age and calculate averaged EQ-5D-based utility weights by quartile at three months and one year. We will categorize age to ensure reliable estimates within each age category.

These weights will then be used as the measure of HRQoL. All patients developing ESRD and requiring dialysis will be assigned an appropriate utility weight based on European norms(17) from the date of first chronic renal replacement forward. HRQoL at three months and one year will be combined with the survival data to report QALYs at one year.

6.3.2.5 Cost-effectiveness analysis

The cost-effectiveness analysis (CEA) will report mean (95% confidence interval) incremental costs, and QALYs at one year associated with a change from SHA RCA for CRRT, overall and for pre-specified subgroups. The CEA will use multilevel generalised linear models that allow for clustering of patients in sites including random effects for both level and slope. Incremental net monetary benefits (INB) at one year associated with a change from SHA to RCA will be estimated valuing incremental QALYs according to a NICE recommended threshold willingness-to-pay for a QALY gain (£20,000) and subtract from this the incremental costs. Missing data will be addressed following a recommended approach of multiple imputation using the MICE algorithm as followed for the primary clinical endpoints (see Section 6.2.2), assuming data are missing at random conditional on baseline covariates, resource use and observed endpoints.

The economic analysis will also project lifetime cost-effectiveness by encapsulating the relative effects of the alternative strategies on long-term survival and HRQoL, combining extrapolations from the patient survival data, with external evidence on long-term survival and HRQoL. We will consider alternative parametric extrapolation and chose the model on the basis of model fit and plausibility when compared with age-gender matched general population survival. Survival will then be extrapolated according to chosen parametric function for the duration of years that parametric curves predicts excess mortality compared to age-gender matched general population, after which we will assume that all cause death rates were those of the age-gender matched general population. We will project lifetime costs by applying morbidity costs estimated at one year over the period of excess mortality. Sensitivity analyses will test whether the results are robust to methodological assumptions (e.g. specification of the statistical model, extrapolation approach, and alternative HRQoL assumptions).

7 Study management and committees

7.1 Role of the ICNARC Clinical Trials Unit

The ICNARC CTU will be responsible for the day-to-day management and running of the study and will act as custodian of the data. Basing the study in ICNARC minimises the movement of electronically held patient identifiable data and comply with ICNARC's existing Confidentiality Agreement Group (CAG) approvals.

7.2 Good research practice

RRAM will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

7.3 Study Management & oversight

All day-to-day management of RRAM will be the responsibility of the Study Management Group (SMG) consisting of the Chief Investigator, the project manager, and co-applicants. The SMG will meet regularly to discuss management and progress of the study and findings from other related research. We will also convene a project oversight group, comprising two of the senior investigators and three independent members including a PPI representative with considerable experience of database/clinical record studies. The oversight group will meet shortly after contracting is complete to scrutinise and advise on the overall project plan and scheduling, and again after 5-6 months to ensure the project is on track. Additional ad hoc meetings will be organised as needed.

8 Ethical and regulatory considerations

8.1 Research ethic committee REC) review and reports

The RRAM study protocol will be submitted for Health Research Authority and REC for approval. In addition, we will also apply to the Confidential Advisory Group (CAG) in order to access patient information without consent. Whilst existing CAG approvals are in place for ICNARC and the Renal Registry to hold their data, the linking of the data requires a new approval. The ICNARC CTU will submit annual progress reports and all amendments to the RRAM study protocol to the REC for review.

8.2 Confidentiality and data protection

The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. ICNARC is registered under the Data Protection Act 1998 and all ICNARC CTU staff undergo data protection and ICH GCP training.

Both national clinical audits involved in this study operate under Section 251 of the NHS Act 2006, permitting the use of patient identifiable data without consent for specified purposes. An application will be made to the HRA Confidentiality Advisory Group to request approval under Section 251 for the creation of the linked pseudonymised dataset for this Study. Prior to data linkage, all necessary approvals will be obtained from the Data Controllers of each data source.

As the study uses existing data and does not involve any change to usual care for patients, an independent Data Monitoring Committee (DMC) will not be required.

9 Study closure

9.1 End of study

The "end of the study" will be when all analyses are complete and the Final Report of the Study is submitted to the funder, at which point the declaration of end of study form will be submitted to the REC by the ICNARC CTU.

9.2 Archiving study data

At the end of the Study, the ICNARC CTU will archive securely all centrally-held study-related documents and electronic data for a minimum of ten years in accordance with the ICNARC CTU Standard Operating Procedure (SOP) on archiving trial/study data based on ICH GCP guidelines. After 10 years, arrangements for confidential destruction of all documents and data will then be made.

10 Sponsorship and Indemnity

ICNARC is the Sponsor for the Study and holds professional indemnity insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

11 Funding

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References

1. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. Crit Care Med. 2009;37(9):2552-8.
2. Jones SL, Devonald MA. How acute kidney injury is investigated and managed in UK intensive care units--a survey of current practice. Nephrol Dial Transplant. 2013;28(5):1186-90.
3. Harris SK, Lewington AJ, Harrison DA, Rowan KM. Relationship between patients' outcomes and the changes in serum creatinine and urine output and RIFLE classification in a large critical care cohort database. Kidney Int. 2015;88(2):369-77.
4. Department of Health. Department of Health. NHS reference costs 2016 [Available from: https://www.gov.uk/government/collections/nhs-reference-costs.
5. Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. Int J Technol Assess Health Care. 2003;19(4):613-23.
6. Harrison D. Risk modelling for quality improvement in the critically ill: making best use of routinely available data 2015 [Available from: https://www.journalslibrary.nihr.ac.uk/programmes/hsdr/141906/#/.
7. Harrison DA, Parry GJ, Carpenter JR, Short A, Rowan K. A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. Crit Care Med. 2007;35(4):1091-8.
8. Harrison DA, Ferrnado-Viva P, Shahin J, Rowan KM. Ensuring comparisons of health-care providers are fair: development and validation of risk prediction models for critically ill patients. Health Serv Deliv Res. 2015;3(41).
9. Bartlett JW, Seaman SR, White IR, Carpenter JR. Multiple imputation of covariates by fully conditional specification: Accommodating the substantive model. Stat Methods Med Res. 2014.
10. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.
11. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol. 2006;59(10):1092-101.
12. Lefrant JY, Garrigues B, Pribil C, Bardoulat I, Courtial F, Maurel F, et al. The daily cost of ICU patients: A micro-costing study in 23 French Intensive Care Units. Anaesthesia, critical care & pain medicine. 2015;34(3):151-7.
13. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673-84.
14. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301-11.
15. Griffiths JA, Morgan K, Barber VS, Young JD. Study protocol: the Intensive Care Outcome Network ('ICON') study. BMC Health Serv Res. 2008;8:132.
16. Hatch R, Young D, Barber V, Harrison DA, Watkinson P. The effect of postal questionnaire burden on response rate and answer patterns following admission to intensive care: a randomised controlled trial. BMC Med Res Methodol. 2017;17(1):49.
17. Eriksson D, Goldsmith D, Teitsson S, Jackson J, van Nooten F. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia. BMC Nephrol. 2016;17(1):97.

Appendix 1: Assessment against Ramsay et al criteria

1.	Intervention occurred independently of other changes over time	Although it is impossible to entirely exclude other unobserved changes over time, our discussions with representatives from ICUs that have introduced RCA have indicated that this is predominantly an isolated change in practice not associated with any other changes.
2.	Intervention was unlikely to affect data collection	The data come from routine data sources and collection has been continuous throughout the study period.
3.	The primary outcome was assessed blindly or was measured objectively	The primary outcome (90-day mortality) is measured objectively.
4.	The primary outcome was reliable or was measured objectively	The primary outcome is measured objectively.
5.	The composition of the data set at each time point covered at least 80% of the total number of participants [ICUs] in the study	The coverage of adult general ICUs in the Case Mix Programme has increased from greater than 80% at the start of the study period to 100% now.
6.	The shape of the intervention effect was pre-specified	We have pre-specified the proposed shape in the analysis plan.
7.	A rationale for the number and spacing of data points was described	We have specified our rationale for using individual patient data rather than collapsing into a time series.
8.	The study was analysed appropriately using time series techniques	Time series techniques are not directly applicable to the proposed data structure, however we will take account of potential autocorrelation and heteroscedasticity through use of robust variance estimators.