Renal Replacement Anticoagulant Management (RRAM)

Statistical and Health Economic Analysis Plan

Version 2.0, 04/11/2019

REC number:	18/SC/0204
CAG reference:	18/CAG/0070
IRAS project ID:	236515
Study sponsor:	Intensive Care National Audit & Research Centre (ICNARC)
Study sponsor reference:	ICNARC/02/08/17
ClinicalTrials.gov number:	NCT03545750
Funder:	National Institute for Health Research, Health Technology Assessment Programme
Funder's reference:	16/111/136
Authors:	Prof David A Harrison Dr M Zia Sadique Dr James Doidge

Role, Name and Position	Signature	Date
Chief Investigator: Dr Peter Watkinson (Associate Professor, Division of Anaesthetics, Critical Care and Theatres, Oxford University Hospitals NHS Trust)		
Head Statistician: Prof David A Harrison (Head Statistician, Intensive Care National Audit & Research Centre)		

Senior Statistician

Dr James Doidge

(Senior Statistician, Intensive Care National

Audit & Research Centre)

Senior Health Economist:

Dr M Zia Sadique

(Assistant Professor in Health Economics,

London School of Hygiene and Tropical

Medicine)

Version history

Version number	Date	Summary of main changes from previous versions
1.0	03/10/2017	N/A
1.1	30/01/2019	Administrative changes and data linkage with PEDW added
2.0	04/11/2019	Prior to database lock. Addition of pre-specified sepsis subgroup. Administrative changes to data collection/analysis wording in line with protocol version 2.1.

Table of contents

1. Abbreviations

CAG	Confidentiality Advisory Group
CCMDS	Critical Care Minimum Dataset
CEA	Cost-effectiveness Analysis
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

2.   Background and rationale

The purpose of this Statistical and Health Economic Analysis Plan (the Plan) is to outline the planned analyses to be carried out to support the completion of the Final Report to the study funder and for inclusion in manuscripts for publication in the scientific literature. Additional exploratory analyses, which may not have been identified in the Plan, may also be performed. Any unplanned analyses not identified in the Plan will be clearly outlined as such in the Final Report/manuscripts. The Plan has been agreed in advance of conducting any analyses.

3.   Aims and objectives

3.1.   Research question

What is the effect of regional citrate anticoagulation (RCA) versus systemic heparin anticoagulation (SHA) for continuous renal replacement therapy (CRRT) in patients treated in an intensive care unit (ICU) on:

- all-cause mortality 90 days after the first ICU admission where CRRT occurred? (primary research question)
- the subsequent development of end-stage renal disease (ESRD)?
- the duration and intensity of care on an ICU?
- cost-effectiveness one year after ICU admission?

3.2.   Study 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 a non-specialist ICU in England and Wales.

4.   Study design

4.1. Overview of study design

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

4.2. Population

4.2.1. 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.

4.2.2. Inclusion and exclusion criteria

Inclusion criteria:

- age ≥16 years;
- admitted to an adult, general ICU in England and Wales participating in the ICNARC Case Mix Programme (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.

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 kidney-pancreas transplantation, identified by the recording of "kidney allograft", "kidney autograft", "pancreas or kidney/pancreas allograft" or "kidney allograft rejection" as the primary or secondary reason for admission to ICU, coded with the ICNARC Coding Method(1);
- primary admission with acute hepatic failure, identified by the recording of: (1) "alcoholic or chronic cirrhosis", "acute alcoholic hepatitis", "drug induced hepatitis or hepatic necrosis", "autoimmune hepatitis", "portal hypertension", "variceal haemorrhage", "acute fatty liver of pregnancy", "infective or ischaemic hepatitis", "portal/hepatic vein occlusion" or "hepatic infarction" as the primary reason for admission to ICU; or (2) "metabolic coma or encephalopathy" or "toxic or drug induced coma or encephalopathy" as the primary reason for admission combined with recording of any of the conditions in (1) as the secondary reason for admission or recording of cirrhosis, portal hypertension or hepatic encephalopathy in the past medical history.

4.3. 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.

4.4. 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.

4.5. Outcomes

4.5.1. Primary effectiveness outcome

The primary effectiveness outcome is all-cause mortality 90 days after the first ICU admission in which CRRT was received. Deaths occurring after discharge from acute hospital will be identified by data linkage with Office for National Statistics (ONS) death registrations, undertaken by the NHS Digital Data Access Request Service (DARS).

4.5.2. Secondary effectiveness outcomes

Secondary effectiveness outcomes are:

- 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;
- bleeding and thromboembolic episodes;
- ICU and hospital length of stay;
- development of ESRD treated by RRT at one year after ICU admission.

Days of organ support (based on the CCMDS) and ICU and hospital length of stay will be obtained from the CMP database. Bleeding (using ICD-10 secondary field codes "R04 Category – Haemorrhage from respiratory passages", "I61 Category – Intracerebral haemorrhage", "I62 Category – Other nontraumatic intracranial haemorrhage"," K92.0 – Haematemesis", "K92.1 – Melaena", "K92.2 – Gastrointestinal haemorrhage, unspecified") and thromboembolic episodes (using ICD-10 secondary field codes "I26.9 – Pulmonary embolism without mention of acute cor pulmonale", "I26.0 – Pulmonary embolism with mention of acute cor pulmonale", "I80 Category – Phlebitis and thrombophlebitis") will be identified from data linkage with Hospital Episodes Statistics (HES). Development of ESRD treated by RRT will be identified from data linkage with the UK Renal Registry (UKRR).

4.5.3. Economic outcomes

The primary economic outcome is the 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 SHA to RCA for CRRT.

The secondary economic outcome is an estimated lifetime incremental net benefit associated with a change from SHA to RCA for CRRT.

Full details on data sources and estimation of the economic outcomes are presented in *Health economic analyses*, below

4.5.4. Subgroup analyses

The clinical- and cost-effectiveness outcomes described above will be analysed in a pre-specified subgroup of patients with sepsis (defined according to the Sepsis-3 criteria).(2)

5.   Sample size

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:

- <u>35 changes from SHA to RCA will be observed within the available data</u>. 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.

- <u>Changes from SHA to RCA will be evenly distributed over the time period of the study</u>. 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.

- <u>15 ICUs will have changed from SHA to RCA prior to the start of the study</u>. 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.

- <u>The distribution of risk of 90-day mortality for patients receiving renal replacement therapy in UK ICUs will follow that of the ICNARC$_{H-2015}$ model for acute hospital mortality in critical care</u>. 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.

- <u>The between ICU standard deviation for 90-day mortality will be 0.22</u>. 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.

- <u>Changing from SHA to RCA will be associated with an odds ratio for 90-day mortality of 0.9</u>. 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.   Data management and data linkage

The flows of identifiable and pseudonymised patient data are outlined Figure 1.

6.1. Data linkage with NHS Digital

The following steps will be followed in order:

Step 1: ICNARC will extract data for eligible patients from the CMP database and provide to NHS Digital a file containing four patient identifiers (NHS number, date of birth, gender and postcode) plus a unique patient identifier specific to the study (Study ID) for records held by ICNARC. In parallel, UKRR will provide NHS Digital with a file containing the same four patients identifiers for patients who are eligible for linkage plus a unique patient identifier specific to the extract (Local ID).

Step 2: NHS Digital DARS will undertake the linkage by matching patient identifiers from the ICNARC and UKRR files to the linked HES/ONS database.

Step 3: NHS Digital will provide UKRR with a linkage file containing the Study ID and Local ID for successfully linked patients.

Step 4: For patients in the linkage file, UKRR will provide ICNARC with a file containing (a) the Study ID and (b) the agreed clinical data from UKRR. (No personal identifiable information will included in this file.)

Step 5: NHS Digital will provide ICNARC with a file containing (a) the Study ID and (b) the agreed clinical data from HES/ONS.

Step 6: ICNARC will link the files received from UKRR and NHS Digital with the clinical data extracted from the CMP database using the Study ID to create the final study dataset.

6.2. Data linkage with NHS Wales Informatics Service (NWIS)

The following steps will be followed in order:

Step 1: ICNARC will provide to NWIS a file containing four patient identifiers (NHS number, date of birth, gender and postcode) plus a unique patient identifier specific to the study (Study ID) for records held by ICNARC.

Step 2: NWIS will undertake the linkage by matching patient identifiers from the ICNARC file to the PEDW database**.**

Step 3: NWIS will provide ICNARC with a file containing (a) the Study ID and (b) the agreed clinical data from HES/ONS

Step 4: ICNARC will link the files received from NWIS with the date from the CMP, UKRR and NHS Digital using the Study ID to create the final study dataset.

Figure 1. Study patient data flows
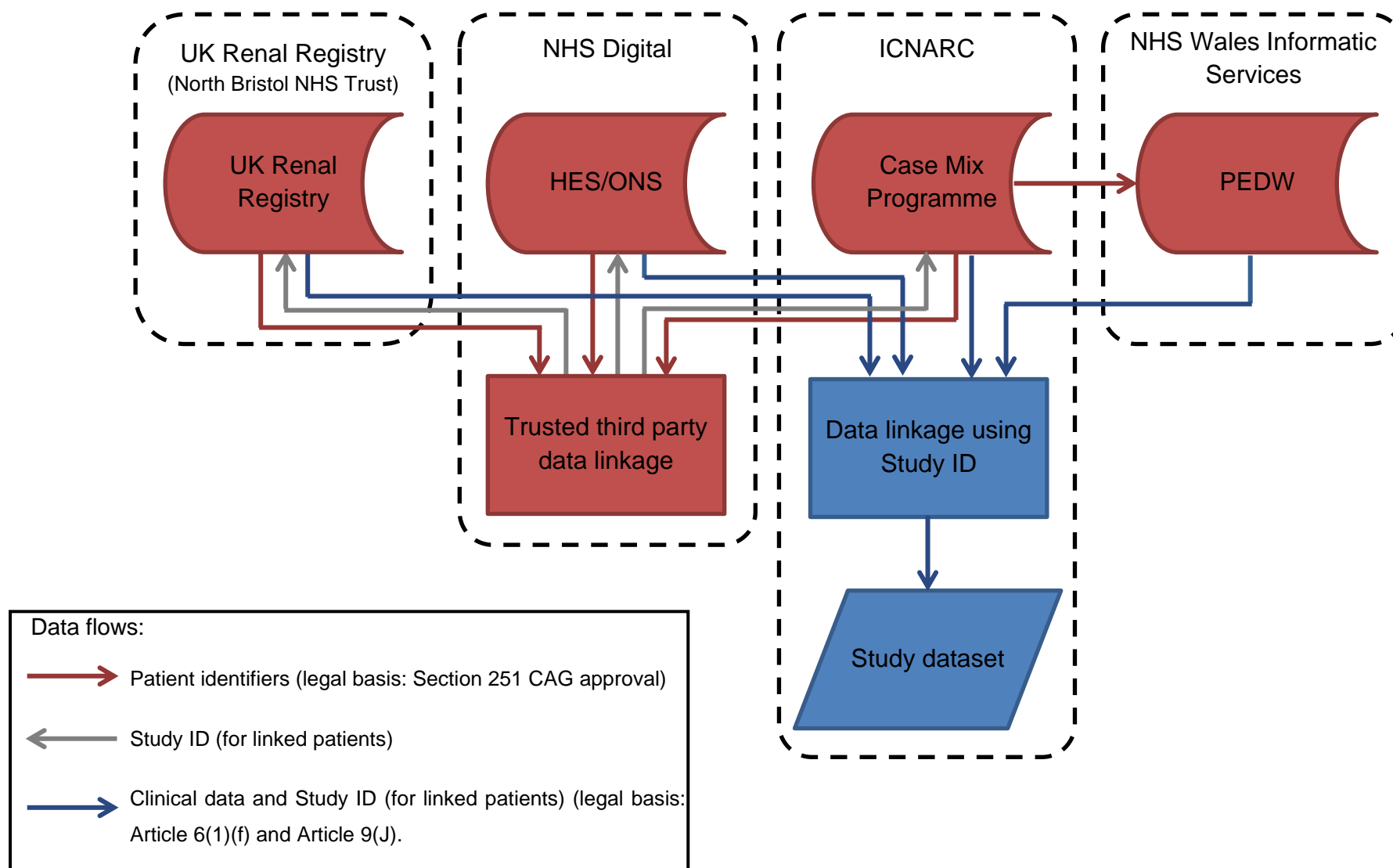
7.   Statistical analyses

7.1. 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. We are not using a standard ITS design, which would typically use a monthly time series aggregated at the ICU level. Given the presence of high quality individual patient data on strong predictors of outcome, the power of the study will be maximised by using an analysis at the individual patient level. However we use the ITS terminology as the same analysis principles apply. This technique is considerably better than simple 'before and after' comparisons. 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(3) (for our assessment of our study against these quality criteria, see Appendix 1).

Random effects multilevel generalised linear models (patients nested within time periods (quarters) nested within ICUs) will be used to estimate the ICU-level effect of transitioning to RCA on trends in patient-level outcomes. Logistic models will be used for binary outcomes and linear models will be used for continuous outcomes. The study will include periods both before and after the switch from SHA to RCA in individual units and a 'control' 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 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. Transition times will be collected in the initial survey. Where longer transition times occurred, these will be accounted for by excluding the corresponding window. If transition is reported to have taken more than a quarter in over 20% of participating units we will amend the length of omitted time for all units accordingly. 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-

Figure 2. Primary impact model
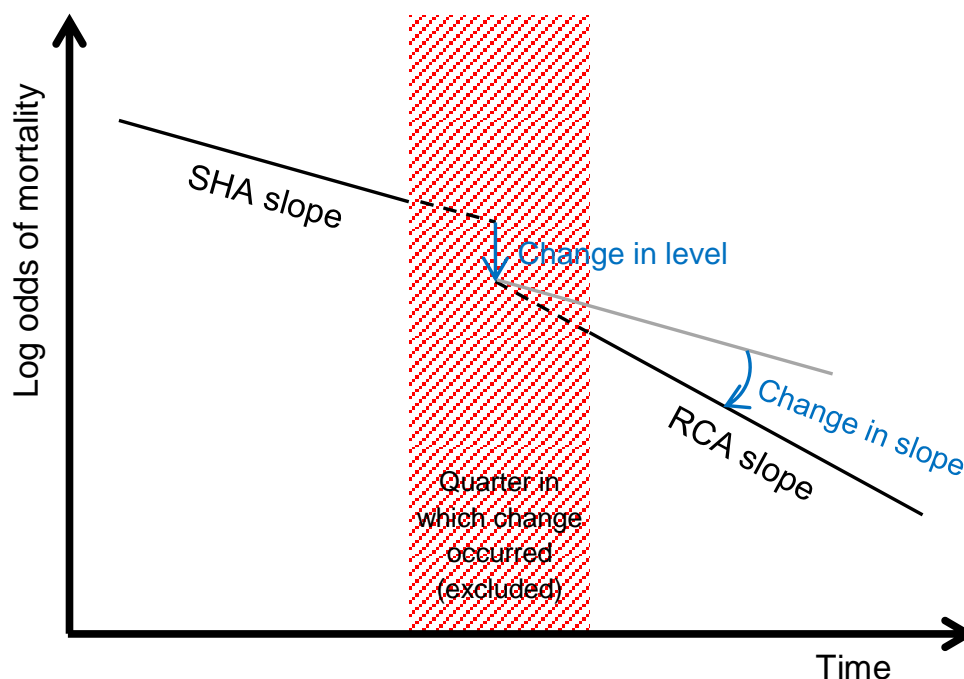
funded project (HS&DR 14/19/06),(4) which builds on considerable previous work in risk modelling in this patient group.(5, 6). This approach has previously been used successfully to evaluate the impact of policy interventions in UK critical care.(7, 8) The results of the regression models will be reported 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.

7.2. 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) This approach was successfully applied when developing the ICNARC risk prediction model.(6) Ten imputed datasets will be generated with the models run in each dataset and results combined using Rubin's rules.(12) To ensure reproducibility of results, the random number seed will be set prior to producing the imputed datasets.

7.3. 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(6) and is developing new models for 90-day and one-year mortality.(4) 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. It is not known what factors are causing the reduction in short-term mortality over time. It is probably improved care, but separating which components of care are causative is not possible.

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

Our study addresses the question of what actually happens when anticoagulation is changed from SHA to RCA in the NHS. It is an effectiveness study designed to show the real-world effect for patients, clinicians and commissioners. CRRT will therefore be viewed as a package of therapy defined by one of two different anticoagulation techniques but encompassing many other aspects. This package includes whatever protocol is used at each site. ICUs changed from SHA to RCA at different times strengthening the natural experiment by reducing the risk of confounding by, for example, changes in policy and practice that take effect across the whole country simultaneously.

8. Health economic analyses

8.1. Data sources for economic outcomes

8.1.1. 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 (see below). CRRT system set-up time and frequency will be obtained from the PICRAM and Oxford University Hospitals computerised information systems datasets (see below).

8.1.2. 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 CMP data. 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.

8.1.3. 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.(13)

8.1.4. Health-related quality of life

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

8.2. 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.

8.3. Measurement of costs

8.3.1. Micro-costing study

Micro-costing of the set-up and running of CRRT using SHA and RCA will be conducted at a representative sample of sites identified from the survey of citrate uptake. Micro-costing will

involve conducting a cognitive walk through (including hierarchical task analysis) with representative clinicians, where 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.(14) The costing will be based on experience of delivering CRRT in a typical ICU. The cost of staff time will be obtained from the Unit Costs of Health and Social Care. Unit costs of anticoagulation drugs will be based on the NHS Business Services Authority Drug Tariff. (15) CRRT fluid costs will be obtained from the manufacturers' quoted prices. Consumable costs will be obtained from the NHS Supply Chain. (16)

8.3.2. 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.

System set-up time will be obtained via the PICRAM database - a Health Information Challenge Fund (HICF)-funded study in Oxford which 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 2009-2015 (PICRAM, HICF 0510 006) and from electronically held data on the CIS for patients treated in Oxford following completion of PICRAM. For patients identified in the CIS as having received CRRT we will extract core demographics (date of admission to ICU, date of birth, weight), all variables describing CRRT, and all variables relating to drugs group and fluid balance for CRRT. After extraction, admission date and date of birth will be converted to age on admission by PICRAM investigators at Oxford, providing an anonymised data set that will be transferred to ICNARC for analysis. The data extraction from the CIS containing admission date and date of birth will be deleted. We can then 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.

8.3.3. Long-term dialysis

Patients identified from UKRR as receiving RRT for ESRD will have their costs estimated dependent on their mode of renal replacement therapy and time to transplant (where applicable) from the date of first renal replacement recorded in the registry. Unit costs of CU/hospital length of stay and dialysis will be obtained from the NHS Reference Costs 2015-16 (13). The costs analysis will calculate total costs per patient up to one year since ICU admission.

8.4. Health-related quality of life and quality-adjusted life years

EuroQuol EQ-5D-3L health-related quality of life (HRQoL) data for patients at three months and one year after ICU discharge will be obtained from the 8000 patient Intensive Care Outcome Network Study (ICON) study.(19) Eligible patients meeting the inclusion criteria will be identified and divided into quartiles of age. Averaged EQ-5D-based utility weights by quartile at three months and one year will be calculated. These weights will 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 (20) from the date of first RRT for ESRD forward. HRQoL at three months and one year will be combined with the survival data to calculate QALYs at one year.

8.5. 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 7.2), 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).

9. References

1. Young JD, Goldfrad C, Rowan K. Development and testing of a hierarchical method to code the reason for admission to intensive care units: the ICNARC Coding Method. Intensive Care National Audit & Research Centre. Br J Anaesth. 2001;87(4):543-8.

2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775-87.

3. 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.

4. 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/#/.

5. 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.

6. 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).

7. Gao H, Harrison DA, Parry GJ, Daly K, Subbe CP, Rowan K. The impact of the introduction of critical care outreach services in England: a multicentre interrupted time-series analysis. Crit Care. 2007;11(5):R113.

8. Hutchings A, Durand MA, Grieve R, Harrison D, Rowan K, Green J, et al. Evaluation of modernisation of adult critical care services in England: time series and cost effectiveness analysis. BMJ. 2009;339:b4353.

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. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: J Wiley & Sons; 1987.

13. Department of Health. Department of Health. NHS reference costs 2016 [Available from: https://www.gov.uk/government/collections/nhs-reference-costs.

14.   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.

15.   NHS Business Services Authority Drug Tariff [Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff.

16.   NHS Supply Chain [Available from: https://www.supplychain.nhs.uk/.

17.   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.

18.   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.

19.   Griffiths JA, Morgan K, Barber VS, Young JD. Study protocol: the Intensive Care Outcome Network ('ICON') study. BMC Health Serv Res. 2008;8:132.

20.   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.

21.   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.

10. 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.