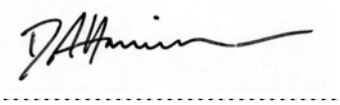
Risk modelling for quality improvement in the critically ill: making best use of routinely available data

REC reference:	**15/WA/0256**
HRA CAG reference:	**15/CAG/0163**
Study Sponsor:	**Intensive Care National Audit & Research Centre (ICNARC)**
Sponsor reference:	**ICNARC/02/07/15**
Study funder:	**NIHR Health Services and Delivery Research (HS&DR) Programme**
Funder reference:	**14/19/06**
ClinicalTrials.gov reference:	**NCT02454257**
Protocol version:	**Version 1.0**
Protocol date:	**12/06/2015**

Role, Name and Position	Signature:	Date:
Chief Investigator: Dr David Harrison Senior Statistician, ICNARC		12/06/2015
For the Sponsor: Keryn Vella Operations Director, ICNARC		12/06/2015

Administration

Sponsor

Study Sponsor:	ICNARC
Address:	Napier House 24 High Holborn London WC1V 6AZ
Contact:	Keryn Vella
Telephone:	020 7831 6878
Fax:	020 7831 6879

Study Management

ICNARC CTU
Napier House
24 High Holborn
London WC1V 6AZ

Tel: 020 7269 9277
Fax: 020 7831 6879
Email: ctu@icnarc.org

Chief Investigator: Dr David Harrison, Senior Statistician, ICNARC

Co-investigators:

Professor Ben Bridgewater	Consultant Cardiac Surgeon, University Hospital of South Manchester NHS Foundation Trust, Honorary Professor of Translational Medicine, University of Manchester
Dr Fergus Caskey	Consultant Nephrologist, North Bristol NHS Trust and Medical Director, UK Renal Registry
Paloma Ferrando-Vivas	Statistician/Risk Modeller, ICNARC
Dr Steve Harris	Clinical Lecturer in Anaesthesia and Intensive Care, University College London
Naomi Holman	Head of Health Intelligence (Diabetes), National Cardiovascular Intelligence Network, Public Health England and Institute of Cardiovascular and Medical Sciences, University of Glasgow
Dr Jerry Nolan	Consultant in Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath NHS Trust and Chair, NCAA Steering Group
Professor Kathy Rowan	Director of Scientific & Strategic Development, ICNARC
Dr Jasmeet Soar	Consultant in Anaesthesia and Intensive Care Medicine, North Bristol NHS Trust
Dr Stephen Webb	Consultant in Anaesthesia and Intensive Care, Papworth Hospital NHS Foundation Trust

Protocol Version History

Protocol:		Amendments:		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
V1.0	12/06/2015	N/A		

Contents

Abbreviations

CMP	Case Mix Programme
DLES	Data Linkage and Extract Service
HES	Hospital Episode Statistics
HS&DR	Health Services and Delivery Research
HSCIC	Health & Social Care Information Centre
ICNARC	Intensive Care National Audit & Research Centre
MRC	Medical Research Council
NACSA	National Adult Cardiac Surgery Audit
NCAA	National Cardiac Arrest Audit
NDA	National Diabetes Audit
NHS	National Health Service
NICOR	National Institute for Cardiovascular Outcomes Research
NIHR	National Institute for Health Research
ONS	Office for National Statistics
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
SMG	Study Management Group

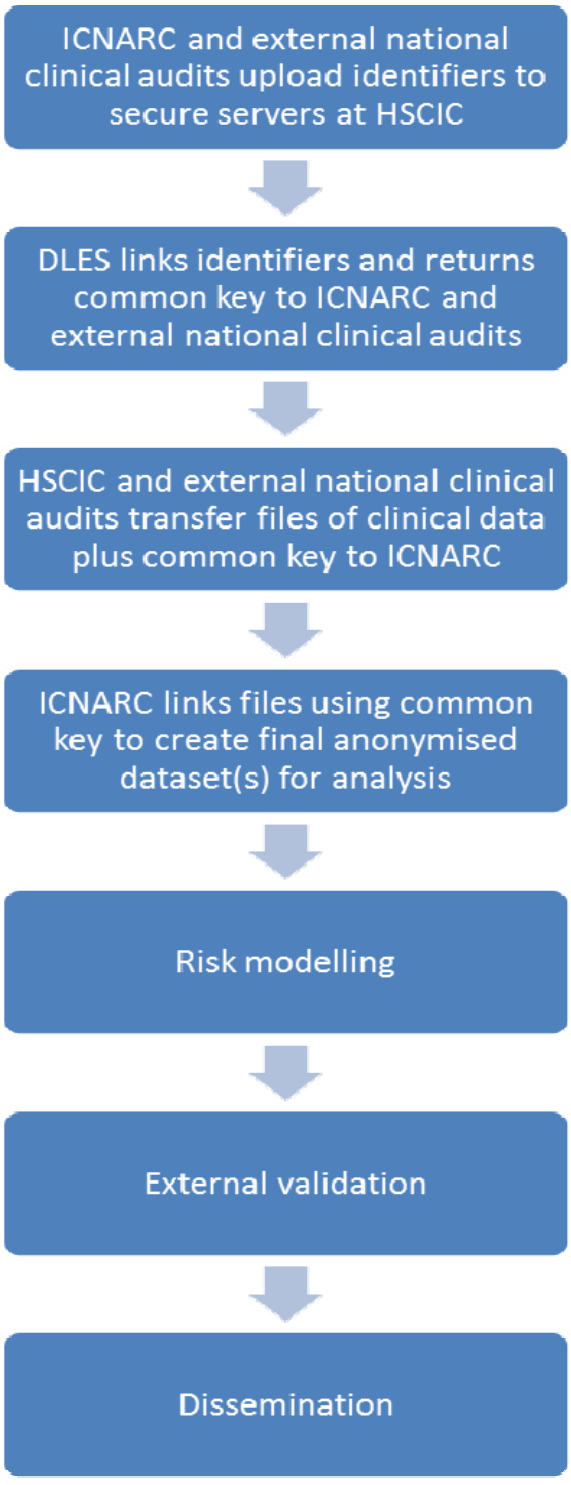
Protocol summary

Synopsis

Title:	Risk modelling for quality improvement in the critically ill: making best use of routinely available data
Short title/acronym:	Risk modelling in the critically ill
Sponsor name & reference:	Intensive Care National Audit & Research Centre, ICNARC/02/07/15
Funder name & reference:	NIHR Health Services & Delivery Research Programme, 14/19/06
Design:	Risk modelling study using existing data
Overall aim:	To better understand the epidemiology of, risk factors for and consequences of critical illness leading to improvements in risk models used to underpin national clinical audits for adult general critical care, cardiothoracic critical care and in-hospital cardiac arrest using data linkage with other routinely collected data sources
Study setting	Adult critical care units, cardiothoracic critical care units and acute hospitals in England and Wales.
Study participants	Patients admitted to an adult critical care unit or cardiothoracic critical care unit or experiencing an in-hospital cardiac arrest in an NHS acute hospital in England or Wales.
Planned sample size	• Approximately 850,000 admissions (700,000 critical care unit survivors) for objective 1. Additional 170,000 admissions (150,000 critical care unit survivors) for external validation. • Approximately 34,000 admissions to cardiothoracic critical care units (31,000 critical care unit survivors) for objective 2. Aditional 2,300 admissions (2,100 survivors) for external validation. • Approximately 56,000 in-hospital cardiac arrests (10,000 survivors) for objective 3. Additional 16,000 in-hospital cardiac arrests (3,000 survivors) for external validation.
Planned study period	24 months
Objectives	1. To improve risk models for adult general critical care by: (1a) developing risk models for mortality at fixed time-points and time-to event outcomes; developing risk models for

	longer term chronic health outcomes of (1b) diabetes and (1c) end-stage renal disease; and (1d) developing risk models for subsequent health care utilisation and costs. 2. To improve risk models for cardiothoracic critical care by: (2a) enhancing risk factor data; (2b) developing risk models for longer term mortality; and (2c) developing risk models for subsequent health care utilisation and costs 3. To improve risk models for in-hospital cardiac arrest by: (3a) enhancing risk factor data; (3b) developing risk models for longer term mortality, health care utilisation and costs; (3c) developing risk models for subsequent critical care utilisation; and (3d) developing risk models for subsequent health care utilisation and costs 4. Immediate translation of the improved risk models into practice through: (4a) adoption into routine comparative outcome reporting for the national clinical audits; and (4b) communication of research output to providers, managers, commissioners, policy makers and academics in critical care

Study flow diagram



1. Background and rationale

High quality care is at the centre of the NHS.[1] National clinical audit has a key role to play in ensuring high quality care, [2, 3]particularly in areas of health care, such as emergency and critical care, where patient choice does not, and cannot, play a significant part. Sophisticated and accurate risk prediction models are key in underpinning fair comparisons among health care providers. They can also enable risk-adjusted observational research and risk stratification in randomised controlled trials.

This study is a follow-on to a previous study that addressed risk prediction modelling in three clinical areas:

- adult general critical care;
- adult cardiothoracic critical care; and
- in-hospital cardiac arrest.

The previous study made substantial steps forward in enabling fair comparisons among health care providers in all three areas, with immediate translation of the research outputs into routine practice, but has also identified important and essential new directions for further epidemiological and methodological research.

1.1. Adult general critical care

In 2005, ICNARC developed and validated the ICNARC model,[4] which underpins the risk-adjusted outcomes reported for the Case Mix Programme (CMP), the national clinical audit for adult general critical care co-ordinated by ICNARC. In the previous research study, the ICNARC model underwent external validation using data from critical care units in Scotland[5] and was subsequently further developed to incorporate better handling of missing data (using multiple imputation), better modelling of physiology (using continuous non-linear modelling) and to make better use of available diagnostic information. This work has resulted in the next generation of the ICNARC model developed using data from over 150,000 admissions to 232 critical care units in a single year, which demonstrates excellent discrimination (*c* index 0.89) and improved risk stratification (net reclassification improvement 23%) in external validation data. This improved model is currently being incorporated into routine reporting for the CMP.

However, The focus of risk prediction modelling in adult general critical care, to date, has been on predicting mortality at discharge from acute hospital. While this is clearly an important and patient-centred outcome, the impact and consequences of critical care goes beyond hospital discharge to include longer-term mortality and morbidity. While routine data on longer-term, health-related quality of life for survivors of critical care are currently not collected/available, national clinical audits of chronic health conditions provide an ideal opportunity to better understand the impact and consequences of critical illness on these specific chronic health conditions gaining some insight into the wider impact of critical care on patients' subsequent health status.

Increased excess mortality following an episode of critical illness has been shown to continue for several years following hospital discharge. Death registrations are maintained by the Office for

National Statistics and made available to health researchers through the Data Linkage and Extract Service (DLES) at the Health and Social Care Information Centre (HSCIC). Data linkage between the CMP and death registrations will enable us to develop risk models to predict longer term mortality following an episode of critical illness.

The occurrence of hyperglycaemia is common among critically ill patients, regardless of diabetes status, and is associated with acute severity of illness and outcomes.[6] Critical illness-related hyperglycaemia has previously been linked with subsequent development of Type 2 diabetes in small cohorts,[7, 8] and data linkage between the CMP and the National Diabetes Audit will permit us to explore this in a much larger cohort and establish whether acute severity of hyperglycaemia or other risk factors are associated with the likelihood of developing Type 2 diabetes.

The occurrence of acute kidney injury (or acute renal failure) is common among critically ill patients and associated with high mortality,[9] and has been strongly linked with subsequent end-stage renal disease.[10] Data linkage between the CMP and the UK Renal Registry will enable us to evaluate this relationship in the UK and develop risk models to predict the requirement for long-term renal replacement among survivors of critical illness in the UK.

Survivors of critical care experience significant morbidity with substantial resultant healthcare resource use and costs.[11] Data linkage with Hospital Episode Statistics (HES) will enable us to estimate the cost of subsequent hospitalisations and its association with severity and/or duration of critical illness and other risk factors.

1.2. Adult cardiothoracic critical care

Cardiothoracic critical care presents particular challenges for risk modelling, with a relatively low risk population, in comparison with other critical care sub-specialties. Patients may present with considerable physiological derangement due to the major insult of cardiac surgery, but not associated with the same increase in risk that would be anticipated in other critical care settings. For this reason, critical care unit admissions following cardiac surgery have been excluded from most previous critical care risk models. In the previous research study, we developed and validated a novel risk model for cardiothoracic critical care.[12] The resulting model, based on 17,000 admissions to cardiothoracic critical care units, had excellent discrimination (c index 0.90) and this new, specific model for adult cardiothoracic critical care is being incorporated into routine reporting for cardiothoracic critical care units in the CMP alongside the main ICNARC model.

For cardiothoracic critical care, our work to date has focussed on the data items available in the CMP – a dataset designed to implement risk models for adult general critical care. Aside from patient demographics, these are almost exclusively post-operative risk factors. However, the majority of admissions to cardiothoracic critical care units are admitted following cardiac surgery and many pre- and intra-operative risk factors may also influence outcome for these patients.[13]The National Adult Cardiac Surgery Audit collects pre-operative risk factors and intra-operative process measures that would provide potentially important additional risk factor information to enhance our risk predictions among the cohort of patients admitted to cardiothoracic critical care units following cardiac surgery and to explore how risk changes along the patient journey.

Linkage to death registrations from ONS will also enable us to extend our risk models for cardiothoracic critical care to predict longer term mortality.

Data linkage with HES will enable us to estimate the cost of subsequent hospitalisations and its association with severity and/or duration of critical illness and other risk factors.

1.3. In-hospital cardiac arrest

Until recently, no validated risk models existed for predicting outcomes following in-hospital cardiac arrest. The National Cardiac Arrest Audit (NCAA), the national clinical audit of in-hospital cardiac arrest coordinated by ICNARC in collaboration with the Resuscitation Council (UK), was therefore established with a dataset including established important risk factors for outcomes following in-hospital cardiac arrest with a view to subsequent development of a risk model. In the previous research study, we developed and validated two novel risk models for in-hospital cardiac arrest.[14] Based on over 14,000 in-hospital cardiac arrests in 122 hospitals, risk models were developed to predict both return of spontaneous circulation (ROSC) greater than 20 minutes and survival to hospital discharge. These models demonstrate good discrimination (c index 0.72 and 0.81, respectively) in external validation data and have enabled risk-adjusted comparisons among hospitals to be included, for the first time, in routine reporting for NCAA.

Simultaneous to our work developing risk models for NCAA, a risk model for predicting hospital mortality following in-hospital cardiac arrest was published from the United States Get With the Guidelines–Resuscitation registry.[15] This identified largely similar risk factors to the NCAA risk models, but included additional predictors not available in the NCAA dataset, most notably pre-existing comorbidities. Data linkage with HES will enable calculation of comorbidity indices from diagnoses and procedural codes recorded during the hospital episode, an approach that has recently been applied successfully in the UK Renal Registry.[16] Combining this information with the existing risk factors will enable us to determine the contribution of chronic health conditions to outcome from in-hospital cardiac arrest with a view to either routinely linking data in the future, or establishing which comorbidity fields are important to collect directly within NCAA.

While many patients do not survive the initial resuscitation attempt, the treatment of those that do requires substantial resources and many patients will be admitted to a critical care unit. Data linkage between NCAA and the CMP will allow us to better understand patterns of critical care resource use and organ support following successful resuscitation and develop prediction models for likely resource use.

Little is known on longer-term outcomes following in-hospital cardiac arrest and data linkage to ONS will enable us to extend our risk models to predict longer term mortality.

Finally, data linkage with HES will enable us to estimate the cost of subsequent hospitalisations and its association with the measured risk factors.

2. Study aim and objectives

The aim of the proposed study is to better understand the epidemiology of, risk factors for and consequences of critical illness leading to improvements in the risk models used to underpin national clinical audits for adult general critical care, cardiothoracic critical care and in-hospital cardiac arrest using data linkage with other routinely collected data sources.

Specific objectives are:

1. To improve risk models for adult general critical care by: (1a) developing risk models for mortality at fixed time-points and time-to event outcomes (by data linkage between the CMP and death registrations from ONS); developing risk models for longer term chronic health outcomes of (1b) diabetes (by data linkage between the CMP and the National Diabetes Audit) and (1c) end-stage renal disease (by data linkage between the CMP and the UK Renal Registry); and (1d) developing risk models for subsequent health care utilisation and costs (by data linkage between the CMP and HES)

2. To improve risk models for cardiothoracic critical care by: (2a) enhancing risk factor data (by data linkage with the National Adult Cardiac Surgery Database); (2b) developing risk models for longer term mortality (by data linkage between the CMP and death registrations from ONS); and (2c) developing risk models for subsequent health care utilisation and costs (by data linkage between the CMP and HES)

3. To improve risk models for in-hospital cardiac arrest by: (3a) enhancing risk factor data (by data linkage between NCAA and HES); (3b) developing risk models for longer term mortality, health care utilisation and costs (by data linkage between NCAA and ONS); (3c) developing risk models for subsequent critical care utilisation (by data linkage between NCAA and CMP); and (3d) developing risk models for subsequent health care utilisation and costs (by data linkage between NCAA, ONS and HES)

4. Immediate translation of the improved risk models into practice through: (4a) adoption into routine comparative outcome reporting for the national clinical audits; and (4b) communication of research output to providers, managers, commissioners, policy makers and academics in critical care

3. Study design

3.1. Design and theoretical/conceptual framework

Risk modelling study linking existing data from multiple sources

3.2. Sampling

The selection of sites is based on those participating in the CMP and NCAA.

The coverage of the CMP is extremely high, with 256 critical care units participating including over 97% of NHS adult general critical care units in England and Wales. We will link data for the period

1 April 2009 to 31 March 2015, enabling exploration of trends and fit of models over time, although only data from the last two years will be used to fit the final models as our previous research has established that the fit of risk models deteriorates over time.[17] This will give a total sample size of over 850,000 admissions (700,000 critical care unit survivors) for exploring trends and fit over time with 330,000 admissions (280,000 critical care unit survivors) for model fitting. As the CMP is an ongoing programme, additional data will accrue while the development work is ongoing. At one year into the study, an additional 170,000 admissions (150,000 critical care unit survivors) will be available and the linkage will be updated providing data for external validation.

Of twenty-seven specialist cardiothoracic critical care units providing Level 3 (intensive) care, eight currently participate in the CMP. From 1 April 2009 to 31 March 2015 we will have a sample size of approximately 34,000 admissions to these units (3,000 deaths) for objective 2. The updated data linkage will include an additional 2,300 admissions (200 deaths) for external validation.

The coverage of NCAA is increasing and now stands at 181 hospitals, including over 75% of acute hospitals in England and Wales. From 1 April 2011 to 31 March 2015 we will have a sample size of approximately 56,000 in-hospital cardiac arrests (10,000 survivors) for objective 3. The updated data linkage will include an additional 16,000 in-hospital cardiac arrests (3,000 survivors) for external validation.

3.3. Setting/context

Adult general critical care units, cardiothoracic critical care units and acute hospitals in England and Wales.

3.4. Data sources

The study will utilise data collected for the CMP and NCAA. The CMP has been established for 20 years and the resulting high-quality clinical database (of over 1.5 million critical care admissions) has underpinned evaluations of policy and practice in critical care.[18] NCAA was established in 2009 as a joint venture between ICNARC and the Resuscitation Council (UK). Data for both audits are collected to precise rules and definitions by trained data collectors and undergo extensive validation, both locally and centrally, for completeness, logicality and consistency. The CMP database has been independently assessed and scored highly by the Directory of Clinical Databases (DoCDat) against their ten domains (describing elements of coverage and accuracy). Similar processes for NCAA were developed building on the knowledge and experience of the successful systems in place for the CMP.

Data from the CMP will be linked with high quality clinical data collected for the National Diabetes Audit, UK Renal Registry and National Adult Cardiac Surgery Audit. Taken together with the CMP and NCAA, these five national clinical audits hold a combined total of over 80 years' experience of managing and reporting on patients' data to improve outcomes in their respective fields.

The National Diabetes Audit (http://www.hscic.gov.uk/nda) is the largest annual clinical audit in the world and is managed by the Health and Social Care Information Centre (HSCIC) working with Diabetes UK and the National Cardiovascular Intelligence Network, Public Health England. The National Diabetes Core audit, covering care processes, treatment targets, complications and mortality for people with diabetes in primary care and specialist services, is now in its ninth year.

Over recent years, the audit has included over 80% of people diagnosed with diabetes in England and Wales.

The UK Renal Registry (http://www.renalreg.com/) was established by the Renal Association and provides a focus for the collection and analysis of standardised data relating to the incidence, clinical management and outcome of end-stage renal disease. The Registry has been in operation since 1995, with 100% coverage of adult renal units in England and Wales since 2007.

The National Adult Cardiac Surgery Audit (http://www.ucl.ac.uk/nicor/audits/Adultcardiacsurgery) collects consecutive operation data from all 35 NHS hospitals in the UK that carry out adult heart surgery. It has been running since 1977, making it the longest running of all UK national clinical audits. The audit is managed by the National Institute for Cardiovascular Outcomes Research (NICOR) at University College London, in association with the Society for Cardiothoracic Surgeons.

4. Data linkage and data management

4.1. Data linkage

Data linkage will be undertaken by the HSCIC Data Linkage and Extract Service (DLES) acting as a 'trusted third party' (see: Study flow diagram). Identifiers (with no associated clinical data) will be uploaded from each national clinical audit to secure servers at HSCIC. DLES will perform the data linkage and will return to each national clinical audit their local identifier (a field that uniquely identifies records within that dataset) together with a common key that can be used to link all records of the same patient across the different datasets. The three national clinical audits external to ICNARC will then transfer to ICNARC an agreed pseudonymised dataset (including the common key) for records that were successfully linked (see Appendix 1). Similarly, DLES will perform a pseudonymised data extract from HES and ONS data and pass these datasets (again including the common key) to ICNARC. ICNARC will produce pseudonymised data extracts from the CMP and NCAA and these will be linked to the datasets provided by the national clinical audits and DLES using the common key. In this way, only pseudonymised data will be linked between the multiple data sources.

Each data provider will retain the files linking their local identifier to the common key to facilitate future research using linked datasets, subject to necessary approvals.

4.2. Data management

The data for this study will be handled under the same security arrangements as for patient identifiable data from the CMP and NCAA. All data will be managed in accordance with ICNARC's Information Security Policy.

Datasets resulting from the linkage process will be stored on secure servers at ICNARC. No identifiable information will be recorded and only the staff involved in the Study will have acces to the datasets.

5. Statistics and data analysis

5.1. Description of statistical methods

5.1.1. Assessing the predictive performance

Throughout the study, risk prediction models will be validated for their discrimination, calibration and overall fit. The following panel of measures will be used to give an overall assessment of model performance.

The discrimination of the model will be estimated by the *c* index (equivalent to the area under the receiver operating characteristic curve) [19, 20]and accuracy will be assessed by Brier's score (mean squared error between outcome and prediction) [21, 22] We will assess calibration graphically with predicted probability on the X-axis and the observed outcomes on the Y-axis in 10 equal-sized risk groups (calibration plot) and by Cox's calibration regression (linear recalibration of the predicted log odds) [23]. The standardised mortality ratio (SMR) with 95% confidence interval (CI) will be calculated to observe the difference between actual and expected mortality by dividing the observed number number of deaths by the number of deaths predicted by the model. Because of the size of the datasets to be used, we will not assess the calibration of the model with the Hosmer-Lemeshow c-statistic because this may lead to misleading conclusions [24].

5.1.2. Internal and external validation

Each newly developed or revised risk prediction model will be validated using the above measures both within the development sample and in independent validation data.

Where a prognostic model is based on a very large sample size and relevant variables are included in the final model, optimism is small and so, the apparent estimates of model performance (*c* index and Brier's score in the development data) are attractive because of their stability[25]. However, to assess optimistic performance within the development data, the percentage of over-fitting will be estimated by the optimism-corrected statistics.

Where existing risk prediction models are modified, the performance of the revised model will be compared with the existing model using reclassification techniques.[26, 27] The improvement in reclassification will be quantified as the Net Reclassification Improvement NRI. We will calculate the NRI both using pre-defined categories of risk and also as a continuous measure (i.e. the proportion with any improvement in predicted risk compared against the proportion with any worsening in predicted risk).

After one year, the data linkage will be updated to provide an additional year of data to serve as independent validation data.

5.1.3. Approach to model development

The model building process will consist of a number of stages described in Appendix 2.

5.1.4. Analysis of outcome measures

The analysis plans will be finalised with input from the Clinical Advisory Groups prior to modelling.

The following approaches for model development will be applied depending on the outcome and objectives of the analysis:

- To model mortality at fixed time-points (hospital discharge, 30 days, 90 days, 1 year), ROSC greater than 20 minutes and hospital survival: logistic regression (including, if appropriate, random effects of critical care unit/hospital).
- To model time-to-event outcomes: standard survival regression methods such as Weibull and Cox regression.
- To handle interval-censored data: Cox proportional hazards models,[28] complementary log-log models using partial likelihood estimation (to permit interval censoring) and discrete-time hazard models.[29]
- To account for both interval censoring of the time-to-onset and competition with death: cause-specific Cox proportional hazards models [30] and illness-death models will be considered.[31]
- To model critical care/hospital resource use and costs: multilevel regression models and log-linear regression models.

5.2. Model specification

5.2.1. Risk models for adult general critical care (objective 1)

5.2.1.1. Mortality at 30-days, 90-days and 1-year and time to death (objective 1a)

Outcome defined as death (from any cause) within 30-days, 90-days or 1-year of admission to the critical care unit and number of days from admission to death, established by data linkage with death registrations from ONS.

Patients included in the models will be all those admitted to a critical care unit and discharged alive from the critical care unit.

5.2.1.2. New diagnosis of diabetes post-critical care (objective 1b)

Outcome defined as recording of the patient in the National Diabetes Audit database with a year of diagnosis in the calendar year after discharge .

Patients included in the model will be all those discharged alive from acute hospital following a critical care unit admission, excluding any with a pre-existing diagnosis of diabetes (as identified from data linkage with earlier years of data from the National Diabetes Audit, diagnostic coding within HES, or by recording of a primary or secondary reason for admission to the critical care unit associated with diabetes, e.g. diabetic ketoacidosis), those registered with a GP practice that did not submit data to the National Diabetes Audit in the subsequent year, and those in whom diabetes is diagnosed shortly after the episode of critical care

5.2.1.3. New diagnosis of end-stage renal disease post-critical care (objective 1c)

Outcome defined as recording of the patient in the UK Renal Registry database with a date of diagnosis of end-stage renal disease within one year following the date of discharge from hospital.

Patients included in the model will be all those discharged alive from acute hospital following a critical care unit admission, excluding any with a pre-existing diagnosis of end-stage renal disease as identified from data linkage with earlier years of data from the UK Renal Registry or by recording of an ongoing requirement for renal replacement therapy for irreversible end-stage renal disease in the CMP database

5.2.1.4. Hospital resource use and costs post-critical care (objective 1d)

Outcome defined as number of days in acute hospital (LOS), either during the original hospital episode (as identified from CMP data) or subsequent hospital episodes (as identified through data linkage with HES). We assigned a cost to every patient recorded in CMP by using the Reference Cost reported by all English hospitals .

5.2.2. Risk models for cardiothoracic critical care (objective 2)

5.2.2.1. Mortality at discharge from acute hospital (objective 2a)

Outcome defined as mortality at discharge from acute hospital (acute hospital mortality), as used for the current risk model.

Patients included in the model will be all those admitted to a participating cardiothoracic critical care unit.

New risk factors, pre- and intra-operative risk factors obtained by data linkage with the National Adult Cardiac Surgery Audit (see Apendeix 1), will be assessed for their optimal functional form (see Appendix 2).

The starting point for the new risk model will be the previously developed risk model using CMP data only.

5.2.2.2. Mortality at 30-days, 90-days and 1-year (objective 2b)

Outcome defined as mortality at 30-days, 90-days and 1-year using the date of death obtained by data linkage with ONS.

Patients included in the model will be all those admitted to a participating cardiothoracic critical care unit.

The starting point for each new risk model will be the risk model developed in objective 2a.

5.2.2.3. Hospital resource use and costs post-critical care (objective 2c)

Outcome defined as number of days in acute hospital, either during the original hospital episode (as identified from CMP data) or subsequent hospital episodes (as identified through data linkage with HES).

Patients included in the risk prediction model will be all those discharged alive from the cardiothoracic critical care unit.

5.2.3. Risk models for in-hospital cardiac arrest (objective 3)

5.2.3.1. ROSC greater than 20 minutes and survival to hospital discharge (objective 3a)

Outcomes defined as ROSC greater than 20 minutes and survival to hospital discharge (hospital survival) from the existing NCAA data, the outcomes for the current risk models.

Patients included in the models will be all patients (aged 28 days or over) who received chest compressions and/or defibrillation following an in-hospital cardiac arrest and were attended by the hospital-based resuscitation team.

The starting point for the new risk models will be the previously developed risk models for each outcome.

New risk factors: pre-arrest risk factors obtained by data linkage with HES, the Charlson comorbidity index [28] and Elixhauser comorbidity measure [29] will be derived from International Classification of Disease (ICD-10) diagnostic codes and Office of Population Censuses and Surveys (OCPS) procedural codes, using methods employed recently by the UK Renal Registry [16], will be assessed for the optimal categorisation of the complex categorical risk factors.

5.2.3.2. Survival to 30 days, 90 days and 1 year and time to death (objective 3b)

Outcome defined as mortality at 30-days, 90-days and 1-year and days from cardiac arrest to death using the date of death obtained by data linkage with ONS.

Patients included in the models will be all patients (aged 28 days or over) who received chest compressions and/or defibrillation following an in-hospital cardiac arrest and were attended by the hospital-based resuscitation team.

The starting point for each new risk model will be the risk model for survival to hospital discharge developed in objective 3a.

5.2.3.3. Critical care resource use post-arrest (objective 3c)

Outcome defined as number of days in a critical care unit (obtained through data linkage with the CMP).

Patients included in the model will be all adult patients (aged 16 years or over) meeting the inclusion for objectives 3a and 3b who survive the initial arrest (ROSC greater than 20 minutes).

As the important risk factors and their relationships with the outcome may be very different from those considered previously, the new risk models for critical care and hospital resource use will be developed, de novo, using the same methods as previously applied to develop the original risk models for ROSC greater than 20 minutes and survival to hospital discharge.

5.2.3.4. Subsequent hospital resource use and costs (objective 3d)

Outcome defined as number of days in acute hospital, either during the original hospital episode (as identified from NCAA data) or subsequent hospital episodes (as identified through data linkage with HES).

Patients included in the model will be all adult patients (aged 16 years or over) meeting the inclusion for objectives 3a and 3b who survive the initial arrest (ROSC greater than 20 minutes).

6. Ethical compliance

6.1. Approval by ethics committee

The Medical Research Council/Health Research Agency (HRA) online decision tool (http://hra-decisiontools.org.uk/ethics/) indicates that approval by an NHS Research Ethics Committee is not required for secondary research using existing pseudonymised data, provided the research team could not identify the participants either directly from the data or from its combination with other information likely to come into their possession. As members of the research team have access to patient identifiable data for the CMP and NCAA, it is not clear that this final condition can be met. An application will therefore be made to an NHS Research Ethics Committee for approval of the study.

6.2. 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.

All five 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. A further 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, including from the Healthcare Quality Improvement Partnership (HQIP) for the two HQIP-funded national clinical audits (National Diabetes Audit and National Adult Cardiac Surgery Audit).

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.

7. Study closure

7.1. 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.

7.2. 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.

8. Study management

8.1. Good research practice

The study will be managed according to the MRC's Guidelines for Good Clinical Practice in Clinical Trials and Good Research Practice: Principles and guidelines, which are based on the principles of ICH GCP. 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.

8.2. Study Management Group

The day-to-day running of the Study will be overseen by a Study Management Group (SMG) consisting of the Chief Investigator, the ICNARC co-investigators, Andrew Fleming (National Audit Data Manager, ICNARC) and a Research Administrator. The SMG will meet at least monthly to review progress.

8.3. Study Steering Committee

The Chief Investigator will report to the Study Steering Committee (SSC), which will monitor progress of the Study against timelines and milestones. The SSC will be chaired by an independent member, Dr David Cromwell, Director of the Clinical Effectiveness Unit, Royal College of Surgeons and Senior Lecturer in Health Services Research, London School of Hygiene and Tropical Medicine.

8.4. Clinical Advisory Groups

For each specific clinical focus of the study, a Clinical Advisory Group will meet regularly (using a combination of face-to-face meetings and teleconference), led by the relevant clinical co-investigators, to provide clinical advice and guidance.

9. 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.

10. Funding

The Study is funded by the NIHR Health Services & Delivery Research (HS&DR) Programme (Project No. 14/19/06).

11. Dissemination

The results of the Study will be widely and actively disseminated.

Results will be presented at the Annual Meeting of the Case Mix Programme and the Annual Meeting of the National Cardiac Arrest Audit and at relevant scientific and health services conferences and meetings.

A Final Report to the HS&DR programme will present a detailed description of the Study and the results along with implications for policy and practice and recommendations for future research. Articles will be prepared for publication in academic peer-reviewed journals and relevant professional journals.

In line with NIHR guidance on maximising the use of data from publicly funded research, the final anonymised, linked dataset will be made available on request for further epidemiological and methodological research.

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Appendix 1 Fields to be included in final pseudonymised data extracts

Case Mix Programme
Common key
Unique hospital identifier (anonymous)
Unique critical care unit identifier (anonymous)
Deprivation quintile
Residence prior to admission to acute hospital
Age (whole years)
Ethnicity
Body mass index
Sex
Date of admission to hospital
Date of admission to the critical care unit
Time of admission to the critical care unit
Cardiopulmonary resuscitation within 24 hours prior to admission to the critical care unit
Location (in)
Classification of surgery
Hospital housing transient location (in)
Prior location (in)
Hospital housing non-transient location (in)
Date of original admission to/attendance at acute hospital
Date of original admission to ICU/HDU
Admission type
Primary reason for admission to the critical care unit
Secondary reason for admission to the critical care unit
Evidence available to assess past medical history
Severe conditions in the past medical history – respiratory
Severe conditions in the past medical history – cardiovascular
Severe conditions in the past medical history – renal
Severe conditions in the past medical history – liver
Severe conditions in the past medical history – metastatic disease
Severe conditions in the past medical history – haematological malignancy
Severe conditions in the past medical history – immunocompromise
Dependency prior to admission to acute hospital
Evidence available to abstract physiology data
Lowest central temperature
Highest central temperature
Lowest non-central temperature
Highest non-central temperature
Lowest systolic blood pressure
Paired diastolic blood pressure (for lowest systolic blood pressure)

Highest systolic blood pressure
Paired diastolic blood pressure (for highest systolic blood pressure)
Lowest heart rate
Highest heart rate
Lowest non-ventilated respiratory rate
Highest non-ventilated respiratory rate
Lowest ventilated respiratory rate
Highest ventilated respiratory rate
Lowest PaO_2
Associate FiO_2 (from arterial blood gas with lowest PaO_2)
Associate $PaCO_2$ (from arterial blood gas with lowest PaO_2)
Associate pH (from arterial blood gas with lowest PaO_2)
Lowest pH
Associate $PaCO_2$ (from arterial blood gas with lowest pH)
Lowest serum bicarbonate
Highest serum bicarbonate
Lowest serum sodium
Highest serum sodium
Lowest serum potassium
Highest serum potassium
Lowest serum glucose
Highest serum glucose
Highest blood lactate
Highest serum urea
Lowest serum creatinine
Highest serum creatinine
Total urine output
Lowest haemoglobin
Highest haemoglobin
Lowest platelet count
Highest platelet count
Lowest white blood cell count
Associated neutrophil count (for lowest white blood cell count)
Highest white blood cell count
Associated neutrophil count (for highest white blood cell count)
Pupil reactivity (left eye)
Pupil reactivity (right eye)
Sedated or paralysed and sedated for whole of first 24 hours in the critical care unit
Neurological status
Lowest total Glasgow Coma Score (GCS)
Associated eye component (for lowest total GCS)
Associated motor component (for lowest total GCS)
Associated verbal component (for lowest total GCS)

Associated intubation status (for lowest total GCS)
Highest level of care received in the first 24 hours in the critical care unit
Number of basic respiratory support days
Number of advanced respiratory support days
Number of basic cardiovascular support days
Number of advanced cardiovascular support days
Number of renal support days
Number of neurological support days
Number of gastrointestinal support days
Number of dermatological support days
Number of liver support days
Number of Level 3 days
Number of Level 2 days
Number of Level 1 days
Number of Level 0 days
Treatment withheld/withdrawn
Status at discharge from the critical care unit
Date when fully ready to discharge
Time when fully ready to discharge
Reason for discharge from the critical care unit
Timeliness of discharge from the critical care unit
Date of discharge from the critical care unit
Time of discharge from the critical care unit
Level of care received at discharge from the critical care unit
Expected dependency post-acute hospital discharge
Brainstem death declared
Date of declaration of brainstem death
Time of declaration of brainstem death
Date of death
Time of death
Location (out)
Hospital housing location (out)
Date of ultimate discharge from ICU/HDU
Status at ultimate discharge from ICU/HDU
Date of discharge from hospital
Status at discharge from hospital
Destination post-discharge from hospital
Date of ultimate discharge from acute hospital
Status at ultimate discharge from acute hospital
Residence post-discharge from acute hospital

National Cardiac Arrest Audit
Common key
Unique hospital identifier (anonymous)
Age (whole years)
Sex
Ethnicity
Date of admission to/attendance at/visit to hospital
Reason for admission to/attendance at/visit to hospital
Date/time of 2222 call
Status at team arrival
Location of arrest
Presenting/first documented rhythm
Date/time resuscitation started
Date/time resuscitation stopped
Reason resuscitation stopped at end of team visit
Transient post-arrest location
Post-arrest location
Status at discharge from hospital
Sedated at discharge from hospital
CPC at discharge from hospital
Method used to assess CPC at discharge from hospital
Date of discharge from hospital
Date/time of death

UK Renal Registry
Common key
ERF patient flag
Date first seen by Renal Physician
Serum creatinine when first seen
Date of renal referral
Date of 1st eGFR of CKD5 (Date of Start of CKD5)
1st eGFR at start of CKD5
Date of 2nd eGFR 90 days later (CKD5)
2nd eGFR 90 days later (CKD5)
Date 1st ERF treatment
Primary disease code (ICD)
EDTA primary renal disease code
Date of last creatinine prior to start of ERF
Last creatinine prior to start of ERF

National Diabetes Audit
Common key

Diabetes Diagnosis Date
Diabetes Diagnosis Type Code
HbA1c (value and date)

National Adult Cardiac Surgery Audit
Common key
Angina status pre-surgery
Dyspnoea status pre-surgery
Number of previous MIs
Interval between surgery and last MI
Previous PCI
Previous cardiac surgery
Diabetes management
Cigarette smoking history
History of hypertension
Actual creatinine at time of surgery
Renal function/Dialysis
History of pulmonary disease
History of neurological disease
History of neurological dysfunction
Extracardiac arteriopathy
Pre-operative heart rhythm
Ejection fraction category
PA systolic
Intravenous nitrates or any heparin
Intravenous inotropes prior to anaesthesia
Ventilated (Pre-Operation)
Cardiogenic shock (Pre-Operation)
Date and time of operation
Operative urgency
Number of previous heart operations
CABG
Valve
Major aortic
Other Cardiac Procedures
Other Actual Cardiac Procedures
Total number of distal coronary anastomoses
Number of valves replaced/repaired
Native aortic valve pathology
Reason for repeat aortic valve operation
Aortic valve procedure
Native mitral valve pathology

Reason for repeat mitral valve operation
Mitral valve procedure
Native tricuspid valve pathology
Reason for repeat tricuspid valve operation
Tricuspid valve procedure
Native pulmonary valve pathology
Reason for repeat pulmonary valve operation
Pulmonary valve procedure
Number of aorta segments operated on
Aortic pathology – Root Segment Code 1
Aortic pathology – Ascending Segment Code 2
Aortic pathology – Arch Segment Code 3
Aortic pathology – Descending Aorta Segment Code 4
Aortic pathology – Abdominal Segment Code 5
Cardiopulmonary bypass
Intra-aortic balloon pump used (pre-operative)
Impeller device used (pre-operative)
Ventricular assist device used (pre-operative)
Other Support device used (pre-operative)
Intra-aortic balloon pump used (intra-operative)
Impeller device used (intra-operative)
Ventricular assist device used (intra-operative)
Other Support device used (intra-operative)
Intra-aortic balloon pump used (post-operative)
Impeller device used (post-operative)
Ventricular assist device used (post-operative)
Other Support device used (post-operative)
Cumulative bypass time
Cumulative cross clamp time
Total circulatory arrest time
Additive Euroscore
Logistic Euroscore

Hospital Episode Statistics – Admitted Patient Care data
Common key
Date of admission
Method of admission
Source of admission
Date of discharge
Destination on discharge
Method of discharge
Beginning of spell

Date episode ended
Date episode started
Duration of spell
End of spell
Episode duration
Episode order
Episode status
Episode type
All diagnosis codes
Primary diagnosis (4 characters)
All operative procedure codes
Main operative procedure code 3 character
Date of operations
Patient classification
Dominant procedure
Healthcare resource group: version 3.5
NHS-generated HRG code
NHS-generated HRG code version number
SUS generated core spell HRG
SUS generated HRG
SUS generated HRG version number
SUS generated spell ID
Code of GP practice
Record Identifier

HES-linked ONS Mortality data
Fact of Death
Date of Death
ICD 10th Revision Coded Cause(s) of Death

Appendix 2 Approach to model development

For each newly developed or revised risk prediction model, we fill adopt the following general approach to model development.

1. Potential predictors will be identified and patterns of missing data within the potential predictors will be explored, with particular attention to the completeness and accuracy of data linkage between the databases. Approaches to handling the missing data will be compared, based on the best performing approaches from previous work.

2. The most appropriate functional form for each potential predictor will be explored, taking into consideration the use of continuous non-linear models (e.g. restricted cubic splines or right-restricted cubic splines) for continuous predictors and appropriate categorisation and structure of categorical predictors.

3. A main effects model will be fitted through a process of deleting terms, re-fitting and verifying, using: likelihood ratio tests to remove non-significant predictors; and the Bayesian Information Criterion (BIC)[30] as the basis to determine which predictors make an important contribution to the fit of the model.

4. The functional form of each predictor included in the main effects model will then be re-examined to confirm if any changes are required based on adjustment for other important predictors.

5. Finally, interactions between the predictors will be introduced based on clinical input to identify and prioritise the potentially important interactions to consider and avoid over fitting, with interactions retained if they have a positive effect on the BIC.

For objectives 2a and 3a: the addition of new predictors to existing models will be considered and then the effect of those predictors previously included in the risk model will be re-assessed to determine whether they still make an important contribution to the model (see above).

For objectives 2b and 3b: the risk model will be re-fitted to the new outcome, predictors that were previously considered but were found not to be important predictors for hospital survival will be re-assessed by adding them to the model and finally the effect of those predictors previously included in the risk model will be re-assessed to determine whether they still make an important contribution to the model (see above).

For objectives1a, 2b, 3b: it is anticipated that predictors representing age, chronic ill health and functional status will have a greater impact on longer term outcomes than on hospital survival, whereas predictors relating to the acute illness will have less impact.