Critical Illness Related Cardiac Arrest (CIRCA): an investigation of the incidence and outcome of cardiac arrest within Intensive Care Units in the United Kingdom.

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Study NHS R&I reference number	4549

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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KEY STUDY CONTACTS

Chief Investigator	Dr Matt Thomas Department of Anaesthesia Southmead Hospital Bristol BS10 5NB Tel: 07551 399000 Fax: 0117 414 9414 Email: matt.thomas@nbt.nhs.uk
Study Management	ICNARC Clinical Trials Unit (CTU) Napier House 24 High Holborn London WC1V 6AZ Tel: 020 7269 9277 Email: CIRCA@icnarc.org
Sponsor	Intensive Care National Audit & Research Centre Napier House 24 High Holborn London WC1V 6AZ Tel: 020 7831 6878 Email: CIRCA@icnarc.org
Funder(s)	Resuscitation Council (UK) 5th Floor Tavistock House North Tavistock Square London WC1H 9HR Tel: 020 7388 4678 Fax: 020 7383 0773 Email: enquiries@resus.org.uk
Study Coordinator	ICNARC
Study Statistician	ICNARC
Co-investigators	Paul Mouncey, Head of Research, ICNARC Dr Doug Gould, Senior Researcher, ICNARC

	Dr Chris Newell, Consultant in Intensive Care Medicine, North Bristol NHS Trust Emma Gendall, Research Nurse, North Bristol NHS Trust

PROTOCOL VERSION HISTORY

Protocol		**Amendments**		
Version no.	Date	Amendment no.	Protocol section (no./title)	Summary of main changes from previous version
2.0	26 June 2020	SA1	3 Study Design	Minor administrative changes.
			5 Recruitment and Consent	Clarifications and minor changes to process for delivering questionnaire follow-up at sites. (5.2 & 5.3)
			6 Data collection	Minor administrative changes. Clarifications and minor changes to process for delivering questionnaire follow-up at sites. (6.3)
			7 Data Management	Clarification on details for study archiving.
			9 Ethical and Regulatory Considerations	Removal of reference to Expert Advisory Group in PPI section.
			11 Study Management	Removal of reference to Expert Advisory Group.
1.1	**15 October 2019**	**N/A**	**9. Ethical and Regulatory Considerations** **10. Study Closure**	**Updated details for REC and CAG approval.** **Updated details for study archiving.**

ABBREVIATIONS

CAG	Confidentiality Advisory Group
CI	Chief Investigator
CIRCA	Critical Illness Related Cardiac Arrest
CMP	Case Mix Programme
CRF	Case report form
CTU	Clinical Trials Unit
EQ-5D-5L	EuroQol 5 Dimension (5 level)
FROM-16	Family Reported Outcome measures 16
GCP	Good Clinical Practice
HDU	High Dependency Unit
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
IHCA	In-hospital cardiac arrest
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
ISF	Investigator Site File
NCAA	National Cardiac Arrest Audit
NHS	National Health Service
NIHR	National Institute for Health Research
OHCA	Out-of-hospital cardiac arrest
PI	Principal Investigator
PPI	Patient and Public Involvement
REC	Research Ethics Committee
ROSC	Return of spontaneous circulation
SOP	Standard Operating Procedure
UK	United Kingdom

STUDY SUMMARY

Study Title	Critical Illness Related Cardiac Arrest (CIRCA): an investigation of the incidence and outcome of cardiac arrest within Intensive Care Units in the United Kingdom.
Internal ref. no. (or short title)	Critical Illness Related Cardiac Arrest (CIRCA)
Sponsor	ICNARC
Funder	Resuscitation Council (UK)
Study Design	Prospective observational cohort study
Study Participants	Adults having cardiac arrest (defined as receipt of chest compressions and/or defibrillation) after admission to an Intensive Care Unit (ICU) participating in the Case Mix Programme in a hospital participating in the National Cardiac Arrest Audit
Planned Size of Sample (if applicable)	100 ICUs
Follow up duration (if applicable)	12 months
Planned Study Period	3 years
Research Question/Aim(s)	The primary research question is: what is the incidence of critical illness related cardiac arrest (defined as IHCA while in the ICU) in adults in the United Kingdom? Secondary research questions are: a) What are the outcomes for critical illness related cardiac arrest? b) What are the risk factors for critical illness related cardiac arrest? c) What risk factors are associated with outcomes (ICU and hospital survival and quality of survival) in patients experiencing critical illness related cardiac arrest? d) What is the quality of life for patients after critical illness related cardiac arrest? e) What is the quality of life for family members of patients surviving critical illness related cardiac arrest?
Inclusion criteria	1. Age 18 years old or more; and either 2. Cardiac arrest (defined as receipt of chest compressions or defibrillation) occurring while in-

	hospital and within intensive care (defined as either ICU, HDU or combined ICU/HDU); or 3. Family member of a patient surviving to discharge from intensive care after a cardiac arrest within ICU
Exclusion criteria	There are no exclusion criteria
Definition of end of study	The end of the study is defined as when all analyses are complete and the results of the study have been submitted.

FUNDING AND SUPPORT IN KIND

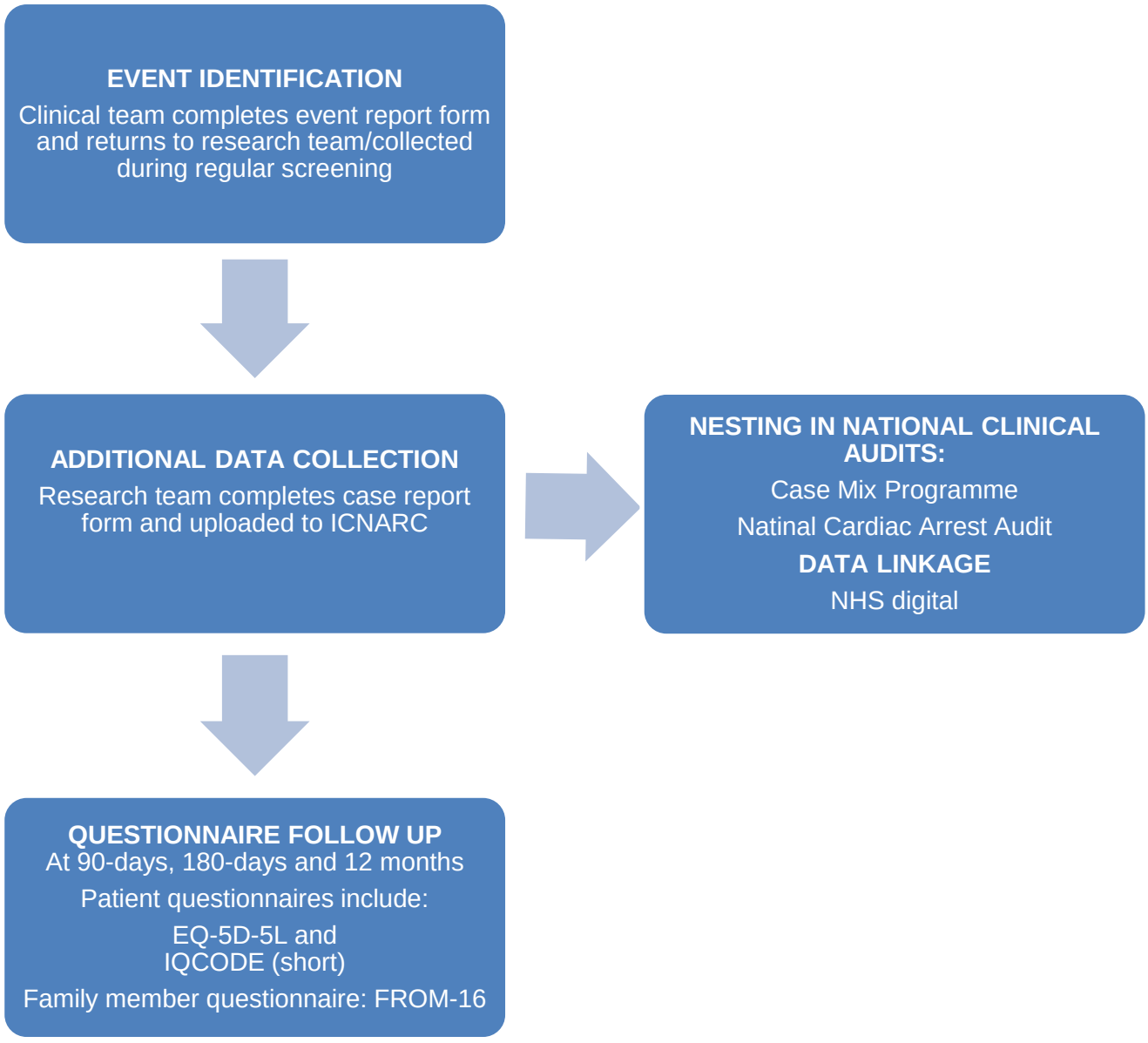
FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Resuscitation Council (UK)	£70,719

ROLE OF STUDY FUNDER

The funder has had no input to study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results and has no control over final decisions regarding any of these aspects of the study.

STUDY FLOW CHART

Figure 1: Study flow diagram



STUDY PROTOCOL

Critical Illness Related Cardiac Arrest (CIRCA): an investigation of the incidence and outcome of cardiac arrest within Intensive Care Units in the United Kingdom.

1 BACKGROUND

Cardiac arrest is often categorised by location, out-of-hospital (OHCA) or in-hospital (IHCA), as there are important differences in population characteristics and aetiology.[1-3] The National Cardiac Arrest Audit (NCAA) was established to audit resuscitation teams in response to IHCA, and collects information about patient characteristics, resuscitation processes, and patient outcomes. However, it does not audit IHCAs that are not attended by the resuscitation team.[4]

Within a hospital, cardiac arrest is usually not further categorised, yet there may be clinically relevant differences between patients treated by different specialities or different locations in hospital.[3] One such is the Intensive Care Unit (here meaning Intensive Care Units, High Dependency Units and combined units that are hereafter collectively referred to as ICUs). Critically ill patients managed in ICUs are experiencing failure of one or more organs and therefore more intensive and invasive therapies are needed to support these failing organs. As a result, ICUs have higher nursing and medical staffing ratios, and monitoring is usually continuous. Moreover, the skill mix of the multidisciplinary team is geared to advanced life support. Thus, the risk of cardiac arrest occurring, the involvement (or not) of the resuscitation team, and the probability of return of spontaneous circulation (ROSC) are all likely to be different to other IHCAs.[5]

Accurate data on cardiac arrests in ICU are lacking. However, a recent systematic review and meta-analysis by one of our team estimates the potential number of events at 22.7 per 1000 admissions (95% 8 / 23 confidence interval 17.4 to 29.6).[6] We have also reported our single centre experience: 75 events in 56 patients with an incidence of 25 IHCA per 1000 admissions. Importantly, those experiencing an IHCA in ICU were different in both case mix and outcome to those not experiencing an IHCA (69.6% ICU mortality compared with 10.5%).[7]

Applying these numbers to Hospital Episode Statistics critical care records for 2016-7, we estimate a total of 7329 cardiac arrest events occurred in UK ICUs in this year.[8] Using data from the Case Mix Programme (CMP) – the national clinical audit covering 100% adult general ICUs – we estimate 3927 IHCA occurred in adult general ICUs in England, Wales and Northern Ireland, based on 173,000 admissions.[9] In the same year, the NCAA reported only 1110 cardiac arrests in ICU in the UK (i.e. those requiring a call to the resuscitation team).[10]

Clearly there is a large knowledge gap - we do not know how many IHCA occur in ICU in the UK nor do we know the impact of an IHCA in ICU on outcome. In addition, we do not know if these IHCAs in ICUs represent an unavoidable consequence of critical illness or, more importantly, whether they can be predicted and/or prevented.

This study aims to determine the incidence and outcomes of IHCA in UK ICUs and explore associated risk factors with ICU and hospital survival and quality of survival following hospital discharge.

2 STUDY AIMS AND OBJECTIVES

This study aims to determine the incidence and outcomes of IHCA in UK ICUs and explore associated risk factors with ICU and hospital survival and quality of survival following hospital discharge.

The primary research question is:

What is the incidence of critical illness related cardiac arrest (defined as IHCA while in the ICU) in adults in the United Kingdom?

Secondary research questions are:

a) What are the outcomes for critical illness related cardiac arrest?
b) What are the risk factors for critical illness related cardiac arrest?
c) What risk factors are associated with outcomes (ICU and hospital survival and quality of survival) in patients experiencing critical illness related cardiac arrest?
d) What is the quality of life for patients after critical illness related cardiac arrest?
e) What is the quality of life for family members of patients surviving critical illness related cardiac arrest?

3 STUDY DESIGN

This is a prospective observational cohort study embedded in the CMP and NCAA.

3.1 Setting

100 adult general critical care units (with variation by geographical area, university teaching status, and size of unit) participating in the CMP and based in hospitals that participate in NCAA.

4 PARTICIPANTS

Adult patients admitted to a participating critical care unit who fulfil the inclusion criteria and their family members.

4.1 Inclusion criteria

The inclusion criteria are:

1. Age 18 years old or more; and either
2. Cardiac arrest (defined as receipt of chest compressions or defibrillation) occurring while in-hospital and within intensive care (defined as either ICU, HDU or combined ICU/HDU); or
3. Family member of a patient surviving to discharge from intensive care after a cardiac arrest within ICU. A family member is defined as a person with a close familial, social or emotional relationship to the patient and is not restricted solely to next-of-kin.

5 RECRUITMENT AND CONSENT

Overview

There are approximately 200,000 patients admitted to CMP participating ICUs annually. It is not reasonable or practical to consent this number of patients for data collection and follow-up in the event of a rare and potentially fatal event. Given the risk factors are unknown and the aim of this study is to describe accurately the incidence of critical illness related cardiac arrest it is not appropriate to target a smaller subset of patients for prospective consent.

5.1 Cardiac arrest event data and data linkage

We will not seek consent to collect limited additional data regarding each cardiac arrest event or for linking to other routinely collected data sets. The minimal additional data to be collected is based on that of the National Cardiac Arrest Audit (which routinely collects data about patients having an IHCA on other wards) and will be embedded in the Case Mix Programme national clinical audit, both of which have existing section 251 approvals for the collection of patient identifiable data without consent.

A significant proportion of patients who experience an IHCA in critical care will not survive the event. We do not believe that contacting family members for a retrospective opinion is justified and do not wish to introduce bias by only recruiting a subgroup of patients (i.e. survivors). Posters and leaflets providing information about the study will be visible and accessible in relative rooms within participating ICUs. Patients and their family members will be able to ‘opt out’ of the study and their data for the purposes of the study.

5.2 Consent for questionnaire follow-up

Patients experiencing an IHCA in critical care and surviving to ICU discharge will be followed-up at 90-days, 180-days and 12-months following the date of the initial IHCA in ICU.

Where possible, patients deemed to have capacity and/or their family members (defined as any person(s) with close familial, social or emotional relationship to the patient) will be given a short information leaflet that briefly explains the purpose of the study and stating that they will be invited to complete short follow-up questionnaires in 90-days, 180-days and 12-months time. Initial contact will be made either on ICU or prior to discharge from hospital and the most appropriate family member identified at this time. If at this point of initial contact the patient/family member indicates that they do not want to receive the questionnaires, no questionnaires will be sent.

Due to the nature of the study, the screening processes to identify IHCA in ICU, and the characteristics of patient recovery and discharge from ICU it is possible that patients will only be identified following discharge. In these cases, sites will check the survival status of the patient and then telephone them 3-4 weeks prior to the 90-day follow-up time point, to establish contact and to obtain permission to send the follow-up questionnaires. Questionnaires will primarily be sent by post, unless another method is requested by a patient or family member, such as email or completing the questionnaire over the telephone with a member of the CIRCA site research team at a mutually convenient time.

After confirming survival status and attempting to contact the patient either in person or via telephone, sites will send the questionnaires packs at 90-days. At the subsequent questionnaire time points (180-days and 12-months), sites will attempt to make contact with patients who could not be reached at 90-days or 180-days. The survival status of the patient must be confirmed prior to sending questionnaires at all time points. The questionnaire packs will include an information sheet and a refusal form to be completed and returned to the site if patients or family members do not wish to participate in the questionnaire follow-up. For patients where no contact could be made either in person or via telephone, their decision on whether to participate can be made by returning either a completed questionnaire or the refusal form.

5.3 Withdrawal from the study

If a patient or family member returns a refusal form or questionnaire to a participating site indicating that they do not wish to participate, no further contact or follow-up will be made. Follow-up data collected up to that point will be retained unless the patient or family member requests otherwise. However, data collected without prior consent on the in hospital cardiac arrest event will not be discarded as for a national clinical audit.

6 DATA COLLECTION

Data collection for CIRCA will be embedded within the CMP and NCAA national clinical audits. Data collection will comprise of in-hospital cardiac arrest event and data linkage and questionnaire follow-up.

6.1 Identification of in-hospital cardiac arrest event

Data will be collected on all patients having an in-hospital cardiac arrest (IHCA, defined as being in receipt of either chest compressions or defibrillation or both) while in the ICU. At the time of the event the clinical team will complete an event report form (paper) based on a modified NCAA dataset and will capture basic event data, such as:

- CMP/NHS numbers;
- ICU/Hospital;
- time and date of arrest;
- whether chest compressions/defibrillation were received;
- other treatments received (e.g. adrenaline and dose);
- presenting rhythm; and
- outcome (including time to return of spontaneous circulation).

The event report form will be returned to or collected by the research team during regular screening by the research team for IHCA events.

A small amount of additional treatment data surrounding the event will be captured on a secure electronic CRF (eCRF) to determine risk factors associated with cardiac arrest in ICU. This will include data such as:

- organ support at the time of IHCA in ICU;
- comorbid conditions; and
- treatment immediately prior to and following IHCA event.

6.2 Data linkage

ICU and hospital outcomes

The patient CMP and NHS numbers (individual patient identifiers) will be collected to allow data linkage with the CMP and NCAA national clinical audits. Baseline demographic and clinical data, and ICU resource usage and survival data will be obtained from the CMP national audit. For patients surviving to ICU and being discharged to the ward, subsequent IHCA events will be identified via data linkage with NCAA. The outcomes from IHCA in ICU will be compared with those from IHCA reported in NCAA.

Long-term outcomes

Data on longer-term outcomes will be obtained from data linkage to routine sources (e.g. NHS Digital) and will include survival status at 12-months, and if applicable, date of death following discharge from acute hospital, and subsequent hospitalisations.

6.3 Questionnaire follow-up

Patients and their family members will be followed-up at 90-days, 180-days and 12-months following patient discharge from the ICU via postal questionnaire packs sent out by sites. The questionnaire packs will include:

- Covering letter
- Patient or family member information sheet detailing the study
- Refusal form
- EQ-5D 5 level health related quality of life questionnaire (EQ-5D-5L) (Patient pack)
- Informant Questionnaire on Cognitive Decline (short form) (Patient pack)
- Family Reported Outcome Measure questionnaire (FROM-16) (Family member pack)

For family members, the following demographics data will also be requested in the form of an additional page to the FROM-16 questionnaire:

- Age group;
- Ethnic group; and
- Relationship to the patient.

In the event of no response to the patient questionnaire, sites will attempt to make telephone contact to find out whether a questionnaire was received four weeks after the questionnaire was sent. If no response is received for the 90-day follow-up, questionnaires will be sent again at all subsequent time points provided no refusal form has been received.

7 DATA MANAGEMENT

IHCA event data and additional treatment data will be collected on paper event and case report forms (CRFs), respectively, prior to entry onto a secure electronic data entry system. Minimal patient identifiable information (CMP and NHS number) will be collected on the CRF to allow for the study team at ICNARC to conduct data linkage with routine sources (CMP, NCAA and NHS Digital). The Site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated by the Site PI to qualified members of the research team and should be recorded on the Delegation Log.

During the conduct of the study, all electronic participant data will be encrypted and all study documents stored securely at the site or the ICNARC CTU, as appropriate. On completion of the study, all participant data (electronic and paper) and other study documents will be archived securely and retained for five years at the site or at the ICNARC CTU, as appropriate.

ICNARC is registered under the Data Protection Act 2018 and all ICNARC CTU staff have undergone data protection and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) training.

8 STATISTICS

Sampling

The best current estimate (from the literature based on single ICU) of UK incidence is that between 5446 and 7329 IHCA occur in ICU in 4066 to 5472 patients annually. Based on this estimate we intend to recruit from 100 ICUs for 12 months, giving us an anticipated number of IHCA of 1320 to 2200 among 986 to 1643 patients from a total of around 75000 admissions. This sample size would enable us to estimate the rate of IHCA with a standard error of approximately 0.5 to 0.6 per 1000 admissions. Survival to hospital discharge (pooled estimate from literature) is 17% and assuming 10% refusal of consent, which represents 151 to 251 patients and families for follow-up. Assuming loss to follow-up or death of a further 10%, the number followed up at one year is estimated to be between 136 and 226 patients and families.

Data analysis

All analyses will be documented in a statistical analysis plan prior to commencing any analysis.

To address the primary research question, the overall incidence of IHCA in UK ICUs and the across site variation will be reported. Factors associated with IHCA in ICU and patient outcomes will be determined using multilevel Poisson, logistic, linear and Cox regression models, as appropriate.

9 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with the study protocol, ICH GCP guidelines, the UK Data Protection Act and Mental Capacity Act, the UK Policy Framework for Health and Social Care Research and ICNARC CTU research policies and procedures.

Central ethical compliance

This study has received a favourable opinion from the South Central - Berkshire Research Ethics Committee and approval from the Health Research Authority. Existing Confidentiality Advisory Group (CAG) approvals are in place for the CMP and NCAA national clinical audits, however a study specific application has been sought and approved by the CAG (19/CAG/0173) in order to access patient information without consent for the purposes of the study. The ICNARC CTU will submit annual progress reports and all amendments to the CIRCA study protocol to the REC and CAG for review, as required.

Local ethical compliance

It is the responsibility of the PI at each site to obtain the necessary local approvals including confirmation of capacity and capability. Evidence of confirmation of capacity and capability must be provided to ICNARC CTU prior to site activation.

Patient and Public Involvement

There are PPI representatives on the Study Management Group.

Data protection and participant confidentiality

All questionnaire follow-up will be conducted by participating NHS sites, minimising the transfer of patient identifiable data outside of the NHS. Identifiable patient data including date of birth, NHS number, and sex will be obtained from the CMP national clinical audit to allow for data linkage to other routine sources. These will be stored securely by the ICNARC CTU in locked cabinet or encrypted electronic file. 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 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. The study has received section 251 approval from the HRA Confidentiality Advisory Group (19/CAG/0173).

10 STUDY CLOSURE

End of study

The “end of the study” will be when all analyses are complete and the results of the study have been submitted for publication, at which point the ICNARC CTU will submit the declaration of end of study form to the REC.

Archiving

At the end of the Study, sites and the ICNARC CTU will archive securely all study-related documents and electronic data for a minimum of five years in accordance with the ICNARC CTU Standard Operating Procedure (SOP) on archiving trial/study data based on ICH GCP guidelines. Following this, a final fully anonymised study dataset will be stored at the ICNARC CTU.

11 STUDY MANAGEMENT

Good Clinical Practice

The study will be managed in accordance with the NHS Health Research Authority UK Policy Framework for Health and Social Care Research.

Study Management Group

The Study Management Group will consist of the Study Coordinator, Chief Investigator and Co-Investigators and PPI representatives. The group will meet regularly to discuss management and review progress.

ICNARC CTU

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.

12 SPONSPORSHIP 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.

FUNDING & REGISTRATION

CIRCA is funded by the Resuscitation Council (UK) and will be registered on ClinicalTrials.gov

13 DISSEMINATION POLICY

Progress of study

Participating sites will be kept informed of study progress through newsletters, emails and telephone. The critical care community will be advised though professional newsletters, meetings and conferences. The public will be informed via the ICNARC website.

Study results

The final study dataset will be held by ICNARC and made available in line with current NIHR guidance once fully analysed and published.

The final report will be submitted to the Resuscitation Council (UK) and for publication in a peer-reviewed journal.

The results of the study will be presented at ICNARC CMP and NCAA Annual Meetings, and national and international conferences in the fields of Resuscitation and Intensive Care Medicine.

14 REFERENCES

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