Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
AIRWAYS-3

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Ionising Radiation for combined review of clinical trial of an investigational medicinal product

( ) Ionising Radiation and Devices form for combined review of combined trial of an investigational medicinal product and an investigational medical device

( ) Clinical investigation or other study of a medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No

b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No

c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- ☑ England
- ☐ Scotland
- ☑ Wales
- ☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

- ☑ IRAS Form
- ☑ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

4a. Will you be seeking data from Hospital Episode Statistics (HES) or the Secondary Uses Service (SUS)?

○ Yes ◉ No

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR Medtech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

◉ Yes ○ No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on

the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN. ***Submission of a Portfolio Application Form (PAF) is no longer required.***

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

◉ Yes ○ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

◉ Yes ○ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
AIRWAYS-3

Please complete these details after you have booked the REC application for review.

REC Name:
Wales REC 1

REC Reference Number:
22/WA/0156

Submission date:
12/05/2022

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Randomised trial of the clinical and cost effectiveness of a supraglottic airway device versus intubation during in-hospital cardiac arrest

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Jonathan	Benger
Post	Professor of Emergency Care		
Qualifications	Doctor of Medicine (University of Bristol) 2002 Fellow of the College of Emergency Medicine 2002 Diploma in Immediate Medical Care (Royal College of Surgeons of Edinburgh) 2002 Diploma in Child Health (Royal College of Physicians) 1997 Diploma in Anaesthetics (Royal College of Anaesthetists) 1996 Fellow of the Royal College of Surgeons of England 1995 Bachelor of Medicine and Bachelor of Surgery (Hons) (University of Bristol)		

	1990 Bachelor of Science (Hons) (University of Bristol) 1987
ORCID ID	0000 0001 6131 0916
Employer	University of the West of England
Work Address	Faculty of Health and Applied Sciences, University of the West of England Frenchay Campus, Coldharbour Lane Bristol
Post Code	BS16 1QY
Work E-mail	Jonathan.Benger@uwe.ac.uk
* Personal E-mail	
Work Telephone	0117 3421497
* Personal Telephone/Mobile	
Fax	

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

Title	Forename/Initials	Surname
Ms	Jessica	Bisset

Address	Research & Innovation UHBW | Level 3, Education and Research Centre Upper Maudlin Street, Bristol
Post Code	BS2 8AE
E-mail	researchapprovals@uhbw.nhs.uk
Telephone	0117 34 20233
Fax	

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	N/A
Sponsor's/protocol number:	ME/2021/7106
Protocol Version:	V1.1
Protocol Date:	09/05/2022
Funder's reference number (enter the reference number or state not applicable):	NIHR 131533
Project website:	https://warwick.ac.uk/fac/sci/med/research/ctu/trials/airways3/

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number
N/A	

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

This is a multi-centre, open-label, pragmatic, individually randomised, parallel group, superiority trial and economic evaluation to determine the clinical and cost effectiveness of a supraglottic airway (SGA) device versus tracheal intubation (TI) during in-hospital cardiac arrest (IHCA). IHCA is a sudden, unpredictable and life-threatening event that affects approximately 1 in 1,000 hospital inpatients, and for which the current survival rate is low. There is clinical equipoise and wide variation in practice regarding the best approach to advanced airway management during IHCA, though some international observational evidence favouring alternatives to TI.
The trial will be conducted in the acute setting in over 100 NHS hospitals throughout the UK. Adult patients who suffer IHCA and require advanced airway management will be randomised by the attending cardiac arrest team to receive either SGA or TI in a 1:1 ratio. We have developed and tested bespoke processes to ensure that study procedures do not delay or interfere with the delivery of life-saving treatments.
An internal pilot study will confirm the feasibility of the trial. An integrated economic evaluation will assess the cost-effectiveness of SGA compared with TI. We are working closely with the relevant clinical teams to ensure the trial can be delivered successfully, and require a total of 4190 participants (2095 in each group) to demonstrate a 3% difference in our primary outcome of the Modified Rankin Scale (mRS) score assessed at hospital discharge or 30 days following IHCA, whichever occurs sooner.
The Modified Rankin Scale is well established as a patient-focussed outcome in cardiac arrest. We will also collect mortality and a range of secondary and safety outcomes, up to six months post IHCA, to assess recovery and the cost effectiveness of the two treatment options. Patient and public involvement has been integral to the design of the study, and this application, and our PPI representatives continue to be fully involved in the delivery, interpretation and dissemination of AIRWAYS-3.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Consent:

This trial will recruit hospital inpatients who experience cardiac arrest and are attended by a dedicated hospital cardiac arrest team. Cardiac arrest is a sudden and unpredictable event that immediately renders the patient unconscious, such that they lack mental capacity. Treatment must be started immediately to maximise the likelihood of patient survival. In this context, it would not be practical to consult a relative or independent registered medical practitioner without placing the potential participant at risk of harm from delaying treatment.
We have identified that the only practical way to proceed with this study is as research that occurs without prior consent, approved by a Research Ethics Committee. We have carefully considered the relevant frameworks developed

by the Health Research Authority in accordance with the Mental Capacity Act 2005, and believe the study meets these requirements. The research team also has extensive experience of successfully completing similar randomised trials in cardiac arrest patients.
Following the emergency, we will inform the participant or their consultee (if the participant lacks mental capacity) of trial enrolment and seek their consent to continue in the study with associated options for further data collection.
The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation including the Mental Capacity Act 2005 and the National Health Service Act 2006 as well as Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the UK General Data Protection Regulation (UK GDPR).
Confidentiality and Data Processing
We are seeking approval from the Confidentiality Advisory Group (CAG) to access and process patient identifiable information without consent for all patients enrolled in the study, regardless of whether they survive the cardiac arrest event.
The majority of patients enrolled in AIRWAYS-3 will die before regaining capacity. It is impossible to obtain consent from a person who has died, and the next of kin cannot give consent in this situation, unless they are the legal Personal Representative or the person administering the estate. As a result, we are applying to CAG to process a limited data set for deceased persons. This is particularly important to ensure that a valid primary outcome is collected for all enrolled patients.
To avoid the risk of significant bias, we are also applying to CAG to process primary outcome data (which is collected routinely) without the patient's consent, and with no option to withdraw from the trial completely. The justification for this is that whilst deceased patients cannot withdraw their data from the study, if those who survive are allowed to withdraw it will create a risk of substantial bias whereby survivors may preferentially withdraw from the study preventing evidence of significant clinical benefit from being detected. In this case we argue that the public interest in completing this research for future patient benefit outweighs the associated breach of confidence.

Information provisions to families of non-survivors:

Survival rates for patients who suffer in hospital cardiac are low, and we anticipate that only 10% of the patients that we enrol will survive to hospital discharge. Following careful consideration with our PPI advisors, the relatives of those who do not survive to ICU discharge will not be informed of trial participation. It is felt the burden (further distress) outweighs the benefit (transparency) since the treatments under study are both part of standard clinical practice and are used routinely during IHCA at present. Relative-focused information sheets will be developed to enable us to respond to those who may request further information about the trial. This model, developed and agreed with our PPI advisors, is based on several previous similar large-scale trials that have successfully enrolled cardiac arrest patients both inside and outside hospital. For example, the AIRWAYS-2 trial successfully enrolled more than 9,000 patients using this model without incident or complaint.

National Data Opt Out:

The national data opt out requires that patients who have previously indicated that they do not wish their data to be used for research are not included in research studies, unless they expressly give their consent to do so. This presents particular challenges for AIRWAYS-3, because the study enrols participants without prior consent, and there is also no opportunity to confirm the patient's national data opt out status prior to enrolment. As a result, we anticipate that we will inadvertently enrol patients who have a national data opt out in place.
Following consultation with our PPI advisors, we propose to withdraw from the study all patients who have registered a national data opt out as soon as possible after enrolment. Only a record of the total number of patients withdrawn from each arm for this reason will be retained to comply with the conventions of CONSORT trial reporting and confirm that the proportion of patients with a national data opt out is the same in the two trial groups (we have no reason to anticipate that it will differ between arms in this randomised trial). However, we cannot allow patients who have survived to preferentially "opt in" to the trial subsequently, because this may introduce significant bias to the results.
Our PPI advisors have therefore recommended that we do not approach survivors who have registered a national data opt out, since we will have withdrawn them in keeping with their previously expressed wishes, we cannot offer them an option to participate and the burden of this information, when recovering from a life-threatening illness, is of no benefit to the individual.

In preparing this ethics committee and CAG application we have worked closed with our patient and public advisory group to ensure that our approach reflects their preferences and views. A letter of support, describing the opinion of our patient and public partners, is appended. CAG will be notified of all amendments to the information provided in our original application. This is because support to process confidential patient information without consent is based on the precise details originally provided to CAG and so any change will not be covered by the existing support until a formal amendment is made and the amendment is supported.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The primary objective of this trial is to determine the clinical and cost effectiveness of SGA versus TI during IHCA by the modified Rankin Scale score assessed at hospital discharge (or at 30 days post-randomisation if the participant remains in hospital).

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

The secondary objective of the trial is to conduct an internal pilot study to confirm the feasibility of the large-scale multi-centre trial.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

In hospital cardiac arrest (IHCA) occurs when the heart stops beating suddenly and is an extreme medical emergency. The estimated incidence of IHCA in the UK, as captured by the National Cardiac Arrest Audit (NCAA), is 1 patient per 1000 hospital admissions.(13) IHCA has significant mortality and morbidity. Current survival to hospital discharge following resuscitation for IHCA in the United Kingdom (UK) is approximately 24%.(1) However, additional UK data collected by members of our research team suggest that survival is closer to 10% in those patients who require advanced airway management (the insertion of a tracheal tube or a supraglottic airway device to ventilate the lungs with supplemental oxygen). Those who do survive may have impaired cognitive and functional abilities that lead to a reduced quality of life and an increased societal burden(15,16).
Following IHCA immediate and effective cardiopulmonary resuscitation (CPR) is central to achieving a good patient outcome. However, chest compressions alone do not provide adequate lung ventilation during prolonged CPR. Effective airway management is essential to ventilate the lungs with supplemental oxygen while minimising the risk of gastric regurgitation and pulmonary aspiration.
Members of the AIRWAYS-3 trial team have recently completed the NIHR-funded AIRWAYS-2 trial of tracheal intubation versus the i-gel supraglottic airway device in OHCA (HTA Project: 12/167/102). This did not detect a significant difference in functional outcome (including mortality) between the two advanced airway management techniques at 30 days, 3 months and 6 months after OHCA.(21,24). Since then updated international resuscitation guidelines support the use of supraglottic airways (SGAs) in settings where intubation success rates are lower.(11) Changes have followed in systems where paramedics manage the airway during out of hospital cardiac arrest (OHCA), but not where doctors are the airway provider including some European pre-hospital systems and all in-hospital cardiac arrests. (25,26) The outstanding clinical question is therefore whether SGAs are superior to tracheal intubation in situations where intubation success rates are assumed to be high.(11) Our national survey and a recent international study both demonstrate substantial practice variation and equipoise in IHCA.(9,27) OHCA is fundamentally different to IHCA in terms of the causes of cardiac arrest, prognosis and time to advanced airway intervention.(28,29) There are also substantial differences between IHCA and OHCA patients; arrests of cardiac cause, and shockable rhythms, are more

frequent in OHCA than IHCA patients, while IHCA is much more commonly due to low oxygen levels making the choice of airway management particularly relevant in the IHCA patient group.(13,28,30) International consensus guidelines and clinical practice make it clear that the results from AIRWAYS-2 cannot be extrapolated to IHCA, and that uncertainty persists regarding the best advanced airway management technique during IHCA.(11)

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Aim: To find out whether insertion of a supraglottic airway device (SGA) is more effective than tracheal intubation (TI) for adults who have suffered a cardiac arrest in hospital and who require advanced airway management.
We will conduct a multi-centre, open-label, pragmatic, individually randomised, parallel group, superiority trial and economic evaluation to determine the clinical and cost effectiveness of SGA versus TI during IHCA. An internal pilot will confirm feasibility.
Research question: In adults with in-hospital cardiac arrest (IHCA) does the use of a supraglottic airway (SGA), compared with tracheal intubation (TI), improve survival with a favourable functional outcome at hospital discharge?
Objectives:
(1) Conduct an internal pilot study to confirm the feasibility of the large-scale multi-centre trial
(2) Determine the clinical effectiveness of SGA management, for adults with IHCA, in terms of survival with a favourable functional outcome and health-related quality of life.
(3) Estimate, in an integrated economic evaluation, the cost-effectiveness of SGA compared with TI.
The primary outcome measure of this trial is functional status at hospital discharge (or 30 days post-randomisation whichever is shorter) as measured by the modified Rankin Scale (mRS)

Secondary outcome measures are:
• Initial ventilation success
• Regurgitation/aspiration during resuscitation
• Return of Spontaneous circulation (ROSC) >20 minutes
• ICU and hospital length of stay
• Health-related quality of life at discharge, 3 and 6 months)
• Survival to hospital discharge, 3 months and 6 months
• Functional status (mRS) at 3 and 6 months

Economic outcomes are: Incremental cost per quality-adjusted life year gained from the perspective of the NHS and personal social services. Within-trial and life-time model estimates will be generated.

Safety outcomes are: adverse events and serious adverse events

Participant identification and screening
Participants will be recruited by NHS hospital clinicians; usually the member of the in-hospital cardiac arrest team who is designated to manage the patient's airway, and who has received appropriate training in trial procedures and Good Clinical Practice (GCP). Our recent national survey shows that this is most commonly a doctor who is training to become a consultant in either anaesthesia or intensive care. This approach will enable study recruitment to be undertaken for all eligible patients on a 24/7 basis.
All clinical trials have inclusion and exclusion criteria referred to as eligibility criteria and which are used to assess whether it safe and suitable for a patient to enter a trial. On arrival at a confirmed IHCA, the designated and trained member of the cardiac arrest team will assess patient eligibility for study inclusion.
To determine eligibility, no additional tests or investigations are required to speed up the process due to the immediate requirement to commence and continue treatment. If the patient requires advanced airway management and is deemed eligible, they will proceed to randomisation. The point of randomisation will be when the allocation is revealed on the electronic progressive web application (PWA or "App") that will be used for randomisation.
Interventions
Participants will be randomly allocated 1:1 to receive either a supraglottic airway device (intervention) or tracheal intubation (control group). Randomisation will take place using a bespoke mobile phone progressive web application (PWA), which has been developed by the programming team at Warwick CTU, and which will be extensively tested before the start of the trial. If, for whatever reason, the PWA does not generate the patient's allocation within 5 seconds of a request being made treatment will proceed as normal, and at the discretion of the treating clinician.
In patients randomised to the intervention group during resuscitation the SGA will be placed according to manufacturer's instructions, with end-tidal carbon dioxide monitoring wherever possible, following an initial period of bag-mask ventilation as required. Up to two attempts at SGA placement will be made and if unsuccessful treatment will proceed as dictated by the treating clinician (including tracheal intubation if indicated). If successful, the SGA should be used until resuscitation efforts cease or return of spontaneous circulation (ROSC) is achieved for >20 minutes, at which point further management will proceed as dictated by the treating clinician.
In patients randomised to the control group during resuscitation tracheal intubation should occur, with end-tidal carbon

dioxide monitoring wherever possible, following an initial period of bag-mask ventilation as required. Two attempts at intubation should be made and if unsuccessful subsequent treatment will proceed as determined by the treating clinician (including placement of a SGA if indicated). If successful, tracheal intubation should continue until resuscitation efforts cease or ROSC is achieved for >20 minutes, at which point further management will proceed as dictated by the treating clinician.
Both interventions are part of standard clinical care in the treatment of IHCA and there are no known additional risks to the participants above routine care.
Consent
The trial will recruit individuals that will be unconscious (having sustained a cardiac arrest) and who require time critical treatment. On this basis, we plan to recruit individuals to the trial without prior consent, in accordance with the Mental Capacity Act 2005. When patients regain capacity, they will be approached to seek their consent to continue participation in the trial. If the patient does not survive the cardiac arrest, relatives will not be informed routinely of trial participation. This approach has been carefully considered and supported by our PPI advisor who felt that the burden (further distress) outweighs the benefit (transparency) since the treatments under study are both part of standard clinical practice and are used routinely during IHCA already.
Data collection and follow up:
Non-identifiable data relating to the management and initial outcome of the cardiac arrest will be collected on the randomisation PWA by the randomising clinician. The National Cardiac Arrest Audit (NCAA), a national clinical audit of in-hospital cardiac arrests in the UK, will provide data on patient characteristics, cardiac arrest characteristics and patient outcomes, supplemented by a small amount of additional data collection using a standardised case report form (CRF) at each site during the patient's hospital stay. Identifiable data will be collected on this CRF by the hospital clinical and research team for data linkage purposes.
Long-term follow up will be conducted at 3- and 6-months following randomisation. Data will be obtained from data linkage sources such as NHS Digital Hospital Episode Statistics, National Cardiac Arrest Audit, Case Mix Programme National and Clinical Audit for adult intensive care. Follow-up for post discharge functional outcomes and health related quality of life will be coordinated by the WCTU and use an established system for contacting patients or their personal consultee.
Timetable for research
48 months in total: set-up (9 months); internal pilot (6 months); recruitment (18 months); final follow-up and analysis (9 months); reporting and dissemination (6 months).
Plan for analysis and report
This study will provide definitive evidence regarding the most effective approach to advanced airway management for IHCA patients. The findings will inform future NHS and international practice.
The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.
Dissemination activities will start as soon as we are permitted to share information about the trial. Audiences include patients and the public, clinicians (doctors, nurses and others), researchers and academic experts, policy makers (NHS England), national and international guideline groups, particularly those related to resuscitation.
A series of outputs will maximise the impact of this research including conference presentations and other dissemination events.
Sample size
We aim to recruit 4190 participants to this trial
PPI involvement
We have an established patient and public research advisory group that has a particular interest in, and experience of, cardiac arrest. This group and other patient and public partners have contributed to the design of this research, and their involvement will be key to completing the trial successfully. Our patient and public contributors have advised on design, consent, data collection and the outcomes measured. They will also assist in disseminating the study's results. Two members of the group have joined the independent trial steering committee, and another PPI representative is invited to all trial management group meetings. Regular reports will be provided to all our patient and public contributors, seeking the benefit of their experience and advice as the research proceeds.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
Patient and public representatives have contributed to the design and development of the trial. A core Patient and Public Research Advisory Group and members of the PCPIE group (a patient, Carer and Public Involvement and Engagement group, based at the Royal College of Anaesthetists which provides patient and public involvement to support researchers in anaesthesia and perioperative medicine) have advised on the study to date. These groups will be updated on trial progress and their active engagement will be sought at all stages of the research. It is anticipated that the core Patient and Public Research Advisory Group will meet at least 12 times during the study, and AIRWAYS-3 will be a standing agenda item with a written report, feedback from the PPI representatives on the Trial Steering Committee and consideration of specific matters arising as well as trial inclusion. Similarly, PPI will be a standing agenda item at all trial-related management and committee meetings, with dedicated PPI representation on the trial TMG.
The PPI representatives will help to develop a detailed dissemination plan for the trial. Public contributors will be involved in developing the materials for presentation of the research and findings to non-academic audiences, including the use of patient and relative stories. PPI contributors will also advise on suitable channels for dissemination of the research findings.

A14-2. Have you tested the acceptability of using patient identifiable data in this study without consent?

Please give details.
The core Patient and Public Research Advisory Group has been particularly engaged in issues relating to the conduct of trials in emergency situations where it is not possible to gain prior consent, and associated data collection and management in this and previous cardiac arrest trials. Group members have discussed and approved a statement setting out their views that accompanies this application. The involvement of these contributors will be key in carrying this trial through to completion.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [x] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [x] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal

- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory
- ☐ Skin
- ☐ Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Adult (known or believed to be age >=18)
In-hospital cardiac arrest, attended by the hospital cardiac arrest team in response to a cardiac arrest call (2222 or equivalent), and including a clinician permitted to undertake tracheal intubation and supraglottic airway placement in that hospital
Undergoing resuscitation requiring advanced airway management

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Patients in the emergency department
Patients already receiving advanced airway management (including a supraglottic airway device) at the time of eligibility assessment
Patients known to be pregnant
Patients with a functioning tracheostomy
Patients who are not a hospital inpatient (e.g. visitors or the general public)

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Eligibility assessment	1	0	<1 min	Conducted by treating hospital clinician at point of cardiac arrest
Randomisation	1	0	<1 min	Conducted by treating hospital clinician at point of cardiac arrest
Notification of enrolment and invitation to participate in follow up (informed consent)	1	0	1-hour	Conducted by research staff - during hospital stay or post discharge
Assessment of functional outcome	3	0	5-minutes	Conducted by research staff at hospital discharge (or 30 days post-randomisation whichever is shorter) - maybe in person, via telephone/video call or via web form.

				Conducted by WCTU at 3 and 6 months - maybe via post, call/video call or via web form
Completion of quality of life questionnaire (EQ-5D-5L) and health services used questionnaire	2	0	10 mins	Conducted by WCTU at 3 and 6 months - maybe via post, call/video call or via web form

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Advanced airway management (SGA)	1	1	10 minutes	by the treating clinician at the hospital location of the cardiac arrest.
Advanced airway management (TI)	1	1	10 minutes	by the treating clinician at the hospital location of the cardiac arrest.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

The study intervention will be used for the duration of the cardiac arrest where patient requires advanced airway management. In most cases this would be for a maximum of one hour. Following randomisation the participation will be followed-up for a period of 6 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Both airway management options (SGA and TI) are in routine use currently during IHCA throughout the UK. The two options will be used in accordance with manufacturer's instructions and accepted clinical practice. Therefore, the interventions under study do not create additional risks beyond current routine care.

Follow-up

Following cardiac arrest, patients may experience changes in their functional status (e.g. how far they can walk, ability to look after their own needs) or mental health (e.g. depression, anxiety). The completion of a health-related quality of life tool may cause participants to reflect on these changes and may cause some anxiety. For in-person assessments (face-to-face/ video-call/ phone-call), research staff at the hospital sites and at WCTU are skilled in conducting research follow-up and able to recognise signs of anxiety or distress. Immediate support may be provided by the research staff, who will (if needed) signpost the participant to other support services. On patient-facing follow-up surveys, we will include information on where additional support can be accessed if needed.

Overall risk

The basis for this trial is that during IHCA, airway management with SGA is clinically superior in terms of survival with a favourable functional outcome and health-related quality of life to TI and thereby improve patient outcomes.

The trial will be overseen by a Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) appointed by the National Institute for Health Research. At least 75% of the TSC will be independent from the study investigators.

All DMC members will be independent of study investigators.
The TSC will provide overall trial supervision on behalf of the trial sponsor and funder, and ensure it is conducted in accordance with regulatory requirements and Good Clinical Practice.
The Data Monitoring Committee (DMC) will monitor safety in this trial. We will regularly prepare reports for the DMC, at an interval to be determined by the DMC. The DMC will determine the nature of any early stopping rules.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

Participants randomised to SGA airway management may benefit from less interruptions to chest compressions and a faster time to ventilation as they can be placed more quickly and require less specialist skills and equipment. This may increase chance of survival and lead to better neurological and health related quality of life outcomes.
Tracheal intubation (TI) has been considered the definitive technique for advanced airway management during IHCA for decades. For participants randomised to tracheal intubation it offers a secure airway with a potentially reduced risks of aspiration of stomach contents into the lungs.
Trial participation will provide important information about the most effective airway management for patients that sustain an in hospital cardiac arrest in the future, both in the UK and across the world. There is no high-quality randomised trial evidence that addresses this research question to date, and considerable equipoise within the clinical community.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Not applicable

A26. What are the potential risks for the researchers themselves? *(if any)*

Most trial participants will unfortunately not survive. This can be emotionally challenging for researchers and may lead to stress and anxiety. Through previous trials in cardiac arrest, we have promoted a culture of openness that encourages discussion and sharing. Where needed, individuals (at both the University of Warwick and NHS hospitals) have access to counselling and other psychological support through occupational health departments.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Patients that sustain an in hospital cardiac arrest will be enrolled into the trial by the treating hospital clinician.
On arrival at the location of the cardiac arrest, the treating hospital clinician (who has been trained in appropriate study procedures and associated GCP) will assess patient eligibility and, where appropriate, randomise the patient to enter the trial using a phone progressive web application (PWA) which will inform the Warwick CTU that the randomisation has occured.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The immediately incapacitating nature of cardiac arrest (sudden loss of consciousness) means that it will not be possible to obtain prospective informed consent from participants. Because of the need for immediate treatment, it will also not be possible to obtain an opinion from a personal or professional consultee. Using the provisions within the Mental Capacity Act 2005 Section 32, approval from a Research Ethics Committee to enrol patients without prior consent will be sought. If the patient survives the initial event, and once they have recovered sufficiently (usually once they are recovering on a general hospital ward), a member of the hospital research team will approach the patient (or if they lack capacity, a consultee) whilst they are still in hospital. They will explain the study and seek consent to continue in the trial.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

The occurrence of a cardiac arrest in hospital is unpredictable. Within seconds of cardiac arrest a person becomes unconscious and thus incapacitated. It is therefore impossible to obtain prior consent from the research participant. Treatment must be started immediately in an attempt to save the person's life. In this setting it will not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying treatment.
Once the initial emergency has passed, consent for continuation in the trial will be obtained from patients who survive or a consultee if the patient lacks capacity. If the patient lacks capacity our preference will always be a personal consultee, however we may approach a professional consultee if no personal consultee can be identified, or a potential personal consultee is unwilling to adopt this role. The patient or consultee will be given adequate time (24 hours if required) to read the participant information sheet and accompanying cover letter (if appropriate) and inform the research staff if they wish to continue to take part. Patients will be offered three consent options:
a. No further participation;
b. Collection of routine data from the patient's health records, but no further contact from the study team and no requests to complete follow-up questionnaires;
c. Collection of routine data from the patient's health records and the completion of follow-up questionnaires.
To avoid the risk of significant bias, primary outcome data will be processed without the patient's consent, and there is no option to withdraw from the trial completely.
Patients who have registered a national data opt out will be withdrawn from the trial as soon as this is identified. Only a count of the total number of patients withdrawn for this reason in each arm will be retained. Survivors with a national data opt out will not be approached or informed about the trial since there is no option for them continue in the study without the risk of introducing significant bias, and withdrawal from the trial ensures that their previously expressed preference has been adhered to.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A30-3. Why is it not practicable for either the researcher's organisation, or the current holder of the information required by the researcher, to seek or obtain patient consent for proposed use of patient identifiable information?

As per A30, due to the urgent need to initiate treatment and the context in which the trial will operate, we do not consider it practical or appropriate to consult a participant, personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment.
Most enrolled patients will die without regaining capacity, making it impossible to gain consent to process identifiable information. For the minority that survive, we require permission from CAG to process identifiable information without patient consent to achieve complete ascertainment of the primary outcome. This is a task in the public interest, without which the research cannot be reliably completed without a risk of significant bias that may invalidate the findings.
Following enrolment, and once the participant regains capacity, they will be approached by research staff to seek their agreement to continue in the study. If the participant lacks mental capacity a consultee will be approached instead.

A31. How long will you allow potential participants to decide whether or not to take part?

As per A30, due to the urgent need to initiate treatment and the context in which the trial will operate, we do not consider it practical or appropriate to consult a participant, personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk to those involved. We believe the only practical way to proceed is to use an emergency waiver of consent model.
Following enrolment, the participant or consultee will be approached by the research team in hospital post ICU discharge or after discharge if they were unable to contact them at this time. They will be given adequate time (around 24 hours in first instance) to read the patient information sheet and accompanying cover letter to inform the research team if they wish to take part or do not want to be contacted further about their participation and/or for data collection to stop.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- (●) Yes
- ( ) No
- ( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with national NIHR supported co-enrolment guidelines. There are many current examples of successful co-enrolment between UK critical care studies, facilitated by these guidelines.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

We will provide alternative arrangements wherever possible, to facilitate enrolment of patients who might not adequately understand verbal explanations in English or who have special communication needs. The trial team will provide translated information sheets in commonly spoken languages to participating hospital sites as required. NHS and local hospital interpreters and translator services will also be used, as and when required, to support the provision of information to participants.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

We will work with local Welsh sites experienced in recruiting patients to research in the acute hospital setting. Sites will be supported in any additional costs in preparing written translations of the PIS and consent documents. In the instance we are unable to translate documents, we will ask local sites to arrange the translations in accordance with the availability of GCP trained staff who will be available to be involved in the research process

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Should there be any subsequent amendment to the final protocol, which might affect the patient's participation in the

trial, then these will be discussed with the participant or their consultee and, if applicable, continuing consent will be obtained using an amended consent form.
If new or relevant information becomes available that suggests one or more trial methods for airway management to cardiac arrest patients is causing harm or is ineffective then this treatment will be stopped.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ◉ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.
- ○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

If a participant who has previously given their consent to continue in the study loses capacity we will continue to collect the primary outcome data from their routine health records (permission for this will be sought as part of the HRA CAG application), but we will not approach them further to complete follow-up questionnaires at 3 and 6 months following the cardiac arrest. If they regain capacity subsequently, we will seek their consent to continue in the study and proceed according to their wishes.

Please complete Part B, Section 6, giving further information about arrangements for including adults unable to consent for themselves.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- ☑ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☑ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers

- ☐ Home or other personal computers
- ☑ University computers
- ☐ Private company computers
- ☑ Laptop computers

Further details:
Warwick Clinical Trials Unit will be responsible for the monitoring of data collection. They will establish a data sharing agreement with the sponsor (University Hospitals Bristol and Weston NHS Foundation Trust) and oversee data sharing with any other external organisations should the need arise

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal identifying consent forms and demographic details will be held in research site files, which will be stored in locations that are restricted and secured so that only the relevant research team has access. Patient identifiable data will only be transmitted to Warwick Clinical Trials Unit from participating sites via a secure online web portal, designed by the WCTU Programming Team. Access to this online web portal will be restricted to authorised members of the research team, via individual logins and IP addresses. Any paper forms with patient identifiable information will be held in secure locked filing cabinets within a restricted access area at participating centres and WCTU.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All trial staff and investigators will adhere to the UK General Data Protection Regulation (UK GDPR). The University of Warwick is registered on the Data Protection Act Register. Access to patient's personal data will be limited to the trial staff, investigators and regulatory authorities. Databases will only be accessed by authorised personnel using individual user accounts. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant number, not by name. Only pseudonymised data will be available to statisticians and health economists for data analysis. Participants will not be identified in any trial reports or publications.

A39. Please specify whether identifiers will be held in the same database as the clinical data, or in a separate database and linked through a unique study or case number. *If held separately, please specify how and at what point the separation will occur. If held in the same database, will the identifiers be encrypted? If so, specify what will be encrypted and who will continue to have access.*

Patient identifiers will be held in the same database as the clinical data, but in a separate table linked through a unique study number. The trial database is encrypted and held on a secure server at the University of Warwick. Access to the table containing patient identifiable data will be restricted to members of the trial team who require access, i.e. only those undertaking data linkage work and contacting patients for follow up.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Personal data will be accessed initially by members of the research team at participating sites, who may sit outside of the patient's direct care team, to identify a patient who has been enrolled into the study, and to complete initial data collection. Personal data will then be entered onto the trial database via the online web portal, which will be accessed at the University of Warwick Clinical Trials Unit by members of the coordinating centre trial team. The access to this will be strictly monitored, and reviewed on a monthly basis.
Consent will be obtained to collect this data, and all participants who have opted out will be withdrawn completely and no data collected.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be analysed by statisticians at Warwick Clinical Trials Unit, University of Warwick.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Professor	Jonathan	Benger
Post	Professor of Emergency Care		
Qualifications			
Work Address	University of the West of England		
	Faculty of Health and Applied Sciences, University of the West of England Frenchay Campus		
	Coldharbour Lane, Bristol		
Post Code	BS16 1QY		
Work Email	Jonathan.Benger@uwe.ac.uk		
Work Telephone	0117 3421497		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
Access to personal data at participating centres may be required for the purposes of sponsor audit or inspection by the regulatory authorities, and must be stored for a period of 10 years or longer if required as per WCTU Standard Operating Procedures. However, names and NHS Numbers etc will be deleted when follow-up/linkage is complete. The remaining pseudonymised data will be retained for 10 years.

A44. For how long will you store research data generated by the study?

Years: 10
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

The local Principal Investigators will maintain all records and documents regarding the conduct of the study. These will be archived by the site for at least 10 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.
The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor will be held and finally archived at the secure archive facilities used by WCTU. This archive will include all trial databases and associated meta-data encryption codes, which will be pseudo-anonymised as soon as possible. The records will be archived for at least 10 years from the close of the study.
At the end of the 10 year period, the data set will be fully anonymised and then retained indefinitely so that it is available for sharing in response to legitimate requests agreed by a research ethics committee, the Chief Investigator and Warwick CTU.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◉ Yes ○ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
Yes - we will provide a gift voucher of £15 when sending out follow up questionnaires on two occasions to reflect the participant's time contribution

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
We will register the trial with the ISCTRN registry (https://www.isrctn.com/).

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☑ Other publication
- ☑ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee

on behalf of all investigators

☐ No plans to report or disseminate the results

☐ Other (please specify)

We will publish lay and professional summaries in written, audible and infographic styles. We will promote the findings at public engagement events. We will disseminate to clinicians through peer-reviewed publications, podcasts, blogs, conference presentations and social media. We will engage policy makers through our membership of key organizations (Resuscitation Council UK and International Liaison Committee on Resuscitation). We will use our trial website, social media and press releases. We will also encourage coverage of the trial in hospital patient-facing materials (e.g. hospital websites, hospital newsletters and email communications). Our patient and public collaborators will support us in developing accessible result summaries (e.g. infographics) which we will share with participants and participating hospitals, and through social media.

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Our publications will report only aggregated data.
In the event that there are very few individuals in a specific category (e.g. <5) that might facilitate identification, we will combine with another category and report as a combined category. In the event that grouping categories is not clinically meaningful, we will report the number of participants in the category as <5, rather than the exact number. We anticipate that this will be unlikely due to the large sample size of the trial.

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.
In our participant information sheet we include details of our trial website address where individuals can find details of the results once the trial is completed and contact information from which more detailed information is available..

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

☑ Independent external review

☐ Review within a company

☑ Review within a multi−centre research group

☑ Review within the Chief Investigator's institution or host organisation

☑ Review within the research team

☐ Review by educational supervisor

☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The research was extensively peer reviewed by the Health Technology Assessment Programme of the National Institute for Health and Care Research (NIHR) prior to funding, and all feedback addressed. The protocol has been reviewed during a preliminary meeting of the independent Trial Steering Committee and Data Monitoring Committee, and all comments incorporated.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☑ Review by independent statistician commissioned by funder or sponsor

☐ Other review by independent statistician

☐ Review by company statistician

☑ Review by a statistician within the Chief Investigator's institution

☐ Review by a statistician within the research team or multi−centre group

☐ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Ranjit	Lall
Department	Warwick Clinical Trials Unit		
Institution	University of Warwick		
Work Address	Gibbet Hill Campus		
	Gibbet Hill Road		
Post Code	CV4 7AL		
Telephone	02476574649		
Fax			
Mobile			
E-mail	r.lall@warwick.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Functional status at hospital discharge (or 30 days post-randomisation whichever is shorter) as measured by the modified Rankin Scale (mRS).

A58. What are the secondary outcome measures?*(if any)*

- Initial ventilation success
- Regurgitation/aspiration during resuscitation
- Return of Spontaneous circulation (ROSC) >20 minutes
- ICU and hospital length of stay
- Health-related quality of life at discharge, 3 and 6 months)
- Survival to hospital discharge, 3 months and 6 months
- Functional status (mRS) at 3 and 6 months

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 4190

Total international sample size (including UK):

Total in European Economic Area:

Further details:
Participants will be randomised in a 1:1 ratio to either the intervention or control group. The sample size was based on a formal sample size calculation.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done,*

giving sufficient information to justify and reproduce the calculation.

To identify a clinically significant difference of 3% (8.5% vs. 11.5%) in the primary outcome requires 4,190 patients (2,095 per group) at the 5% level for statistical significance and 90% power.
The primary outcome is the modified Rankin Scale score (mRS), which is a 7-point scale that is widely used in cardiac arrest research and often dichotomized into 0-3 versus 4-6 categories, with 0-3 score categories approximating the proportion of patients with a 'good' functional outcome and 4-6 score categories approximating the proportion of patients with a 'poor' functional outcome at hospital discharge.(21,22)
Survival to hospital discharge is 24% among all IHCA patients, but additional analysis of these audit data suggest that survival may be as low as 10% in those receiving TI.(9) This is because cardiac arrests of a shorter duration are both less likely to require advanced airway management and less likely to have a poor outcome.(12,18) The sample size is based on mortality, for which data are available. This is not identical to our primary outcome (for which data are not available), however the mRS is dominated by mortality (score 6) in this population, because the fatality rate approaches 90%.
In terms of the clinically relevant difference, the best available observational evidence shows an absolute difference in survival to discharge of 3.1% (19.4% vs. 16.3%) favouring alternatives to TI.(10) Our recent national survey demonstrated that current practice is a mixture of TI and SGA use,(9) and it is therefore assumed that the baseline survival of 10% comprises an equal mix of TI and SGA patients. The 3% minimum clinically significant difference around this baseline of 10% has been set accordingly (8.5% vs. 11.5%). To demonstrate this effect size of 3% difference (8.5% to 11.5%) in patients with a 'good' functional outcome between the interventions, requires a total sample of 4,190 patients (90% power; type I error 5%).

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Patients will be randomised 1:1 to SGA or TI. Randomisation will take place using a bespoke mobile phone progressive web application (PWA), which has been developed by the programming team at the Warwick CTU. The PWA functions both synchronously (on-line) and asynchronously (off-line) to address any problems with data connectivity that may exist in participating hospitals, and to ensure there is no delay in the randomisation process. If the patient is deemed eligible pressing a single button on screen will immediately display the allocation, and irrevocably enrol the patient. If, due to a technical or other failure, the PWA does not display an allocation within five seconds the patient will be treated according to usual care and the clinical judgement of the cardiac arrest team. If, despite technical failure, the allocation is recorded by the PWA the patient will be included in the study under the "intention to treat" principle, whereas if no allocation is recorded the patient will not be included in the study. Following the IHCA a small additional amount of non-identifiable patient data will be entered to the PWA by the enrolling clinician and automatically uploaded to WCTU. WCTU will then alert the research team at that hospital site who will proceed with patient identification and follow-up. Preparatory work by the trial team including interviews and simulations has demonstrated that this approach is clinically and technically feasible; it will be tested further during the internal pilot study.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The primary statistical analysis will be by intention to treat amongst those randomised to TI versus SGA. The primary outcome rate will be assessed using a mixed-effects logistic regression model with hospital site as a random effect and adjustment for important fixed covariates. Secondary outcomes which are categorical will be analysed in a similar way (using mixed-effects logistic regression models) and continuous secondary outcomes will be assessed using mixed-effects linear regression models. Results will be reported using odds ratio or mean difference with 95% confidence intervals.
Crossover: Crossover will be assessed in two ways:
(i) impact on the statistical power of the study: due to the contamination effect in patients who crossover from one intervention to another, there is likely to be a reduction in the study power. We will examine the loss of power, using power curves and different degrees of crossover, pivoted around the observed crossover rates,(38) and assess this at the end of the pilot study as well as presenting these to the DMC at each 6-monthly analysis.
(ii) for the final analysis, we will use inverse probability censoring weighted (IPCW) analysis to account for crossovers, using the primary outcome measure.

The DMC and TSC will assess recruitment, the interim analyses in terms of the statistical monitoring, data completeness and integrity, compliance to the intervention (i.e. crossover) and deviations from protocol. Formal interim analyses will be planned to assess early stopping either for efficacy or harm during the main trial, whilst maintaining

the type I error rate of 5%. The following stopping rules are recommended and will be discussed further with the DMC: when approximately 10% (early monitoring) and 50% (mid-way monitoring) of the total patient data are available. The O'Brien and Fleming boundaries will be used to assess the primary outcome at each of the formal interim analyses,(46) as these methods will preserve the overall type I error rate of 5% and account for the fraction of data available as well as the unequal spacing in the analyses.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Associate Professor	Sarah	Voss
Post Qualifications	Associate Professor in Emergency Care		
Employer	University of the West of England		
Work Address	Coldharbour Lane, Bristol		
Post Code	BS16 1QY		
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Fax			
Mobile			
Work Email	Sarah.Voss@uwe.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Keith	Couper
Post Qualifications	Assistant Professor in Emergency and Critical Care		
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Post Code	CV4 7AL		
Telephone			
Fax			
Mobile			
Work Email	K.Couper@warwick.ac.uk		

	Title	Forename/Initials	Surname
	Professor	David	Harrison
Post Qualifications	Head Statistician		
Employer	Intensive Care National Audit & Research Centre		
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
Professor	Jerry Paul	Nolan

Post Qualifications	Professor of Resuscitation Medicine
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Fax	
Mobile	
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Title	Forename/Initials	Surname
Professor	Gavin	Perkins

Post Qualifications	Director of Warwick CTU and Professor of Critical Care Medicine

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Title	Forename/Initials	Surname
Dr	Behnaz	Schofield

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Title	Forename/Initials	Surname
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Post Qualifications	Consultant in Anaesthetics & Intensive Care Medicine
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Title	Forename/Initials	Surname
Professor	Stephen	Brett

Post Qualifications	Professor of Critical Care
Employer	Imperial College of Science, Technology and Medicine
Work Address	Exhibition Rd, South Kensington, London
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Title	Forename/Initials	Surname
Dr	Laura	Goodwin

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Title	Forename/Initials	Surname
Professor	Ranjit	Lall

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Title	Forename/Initials	Surname
Dr	Katie	Samuel

Post Qualifications	Consultant Anaesthetist
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Title	Forename/Initials	Surname
Dr	Douglas	Gould

Post Qualifications	Senior Researcher
Employer	Intensive Care National Audit & Research Centre

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Fax	
Mobile	
Work Email	Doug.Gould@icnarc.org

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University Hospitals Bristol and Weston NHS Foundation Trust
Given name	Jessica
Family name	Bisset
Address	Research and Innovation University Hospitals Bristol and Weston NHS Foundation Trust,
Town/city	Bristol
Post code	BS2 8AE
Country	
Telephone	0117 342 0233
Fax	
E-mail	researchapprovals@uhbw.nhs.uk

Legal representative for clinical investigation of medical device (studies involving Northern Ireland only)
Clinical Investigations of Medical Devices that take place in Northern Ireland must have a legal representative of the sponsor that is based in Northern Ireland or the EU

Contact person

Name of organisation

Given name
Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
Address	University of Southampton Alpha House, Enterprise Road Southampton,
Post Code	SO16 7NS
Telephone	
Fax	
Mobile	
Email	

Funding Application Status: (•) Secured ( ) In progress

Amount: £2,577,946.97

Duration
Years: 4
Months:

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
National Institute for Health Research HTA Programme

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

(●) Yes ( ) No

Name: Warwick Clinical Trials Unit

Type of organisation:
( ) NHS (●) Academic ( ) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: The study will be conducted according to defined Warwick SOPs.

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (●) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
		Diana	Benton
Organisation	University Hospitals Bristol and Weston NHS Foundation Trust		
Address	Upper Maudlin Street, Bristol		
Post Code	BS2 8AE		
Work Email	researchapprovals@uhbw.nhs.uk		
Telephone	0117 342 0233		
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

West of England

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/01/2022
Planned end date: 31/12/2025
Total duration:
Years: 3 Months: 11 Days: 31

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☐ Scotland
- ☑ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 120

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	90
☑ NHS organisations in Wales	30
☐ NHS organisations in Scotland	
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	120

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

A Trial Monitoring Plan will be developed using Warwick CTU SOPs by the trial team and approved by the CI, a member of the QA team and the sponsor. A risk based proportionate approach will be outlined in the monitoring plan to facilitate remote and off-site monitoring if required.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

The DMC and TSC will assess recruitment, the interim analyses in terms of the statistical monitoring, data completeness and integrity, compliance to the intervention (i.e. crossover) and deviations from protocol.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

Formal interim analyses will be planned to assess early stopping either for efficacy or harm during the main trial, whilst maintaining the type I error rate of 5%. The following stopping rules are recommended and will be discussed further with the DMC: when approximately 10% (early monitoring) and 50% (mid-way monitoring) of the total patient data are available. The O'Brien and Fleming boundaries will be used to assess the primary outcome at each of the formal interim analyses, as these methods will preserve the overall type I error rate of 5% and account for the fraction of data available as well as the unequal spacing in the analyses.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (NHS sponsors only)

☐ Other insurance or indemnity arrangements will apply (give details below)

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☐ Other insurance or indemnity arrangements will apply (give details below)

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

◉ Yes ○ No

If Yes, please give details of the compensation policy:
This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

◉ Yes ○ No ○ Not sure

B. All research other than CTIMPs

In this sub-section, an adult means a person aged 16 or over.

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

In hospital cardiac arrest

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

This trial will recruit adults who have suffered a cardiac arrest whilst they are a hospital inpatient. In hospital cardiac arrest is a sudden and unpredictable event that immediately renders the patient unconscious and incapacitated. It is not possible to obtain consent before the cardiac arrest occurs, and this research question cannot be addressed in a population that has mental capacity.
The time-critical nature of cardiac arrest means that the immediate priority is effective treatment by hospital staff, and this trial seeks to improve the treatment that is delivered to this high-risk patient group to improve long-term outcomes (currently most patients do not survive to leave hospital). As a result, it is not reasonably practicable to consult either a personal or professional consultee about trial enrolment as this would distract and delay the treating clinicians.
The only practical way to proceed is to use a model of research without prior consent, approved by a Research Ethics Committee and the Health Research Authority (HRA). We have carefully considered the relevant legislation, and this proposal has been built on previous successful research in cardiac arrest patients that has been completed by the Chief Investigator and other members of the research team.

B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

If a participant survives the initial cardiac arrest, and begins to recover, we will approach them to seek their consent to continue participation in the trial. Since the intervention is completed in the first 60 minutes of the cardiac arrest, and before the patient has any opportunity to regain capacity, our patient and public advisors have indicated that they do not feel this approach is urgent, and should wait until the patient is recovering on a general ward. Research staff at each hospital site will liaise closely with the clinical team that is responsible for a recovering patient to establish whether they have capacity, and also the optimal time to approach them. Clinical staff caring for patients in hospital wards are trained to assess capacity, and routinely do so as part of their delivery of day-to-day care. Furthermore, research staff at each site are also trained in, and familiar with, capacity assessment in hospital patients. The approach to each individual will be bespoke and staged over a period of time in response to that person's needs and understanding, and accepting that capacity can fluctuate. If a participant consistently lacks capacity an appropriate consultee will be identified and approached.

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

◉ Yes ○ No

If Yes, please indicate the nature of this benefit. You may refer back to your answer to Question A24.

Please refer to A24. This research aims to improve the outcome for adult patients who suffer a cardiac arrest whilst a hospital inpatient. All cardiac arrest patients are unable to consent for themselves, and therefore have the potential to benefit from this research.

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

◉ Yes ○ No

If Yes, please explain how the research will achieve this:

AIRWAYS-3 will provide high-quality evidence as to the optimum approach to advanced airway management during in-hospital cardiac arrest. The trial results will directly inform clinical practice internationally.

B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

◉ Yes ○ No

If Yes, please give an assessment below. Highlight any risk, burden or discomfort specific to these participants and say what will be done to minimise it. You may refer back to your answers to Questions A22 and A23.

Please refer to questions A22 and A23

Questions B7 and B8 apply to any participants recruited in England and Wales.

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research.

If the participant lacks capacity to make a decision about ongoing trial participation, the researcher will approach a personal consultee who meets the criteria described in the Mental Capacity Act 2005. The researcher will provide information about the trial, as well as the participant information sheet and a covering letter. The consultee will be given adequate time to review the information sheet and an opportunity to ask questions. The consultee will be asked to consider what decision the participant is likely to have made if they had mental capacity.

If no personal consultee is available, researchers will approach a professional consultee who is not connected with the conduct of the trial. The same process, as described for the personal consultee, will be followed.

The consultee may decide it is not an appropriate time to discuss the trial, or they may decide that the participant would not want to take any further part in the research. If this is the case their feelings will be respected and their decision about taking part will be recorded.

If an initial approach is made to a professional consultee and a personal consultee subsequently becomes available, then the opinion of the personal consultee will be sought. This will override any decision made by the professional consultee.

The consultee's opinion regarding the participant's likely views will be recorded on a signed form, counter-signed by the staff member receiving the opinion. This form may be signed physically or electronically, however if neither of these are possible a verbal opinion may be recorded by the staff member and witnessed by one other person.

If an initial approach is made to a personal or professional consultee and the participant subsequently regains capacity, the participant's consent will be sought. This will override any opinion given by the personal or professional consultee.

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?

◉ Yes ○ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or advice from a consultee as soon as practicable thereafter.

Please refer to B2

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

Patients that survive
For participants that survive and do not have mental capacity we will approach a consultee. A personal consultee is our

preferred option, however if no personal consultee is available, we will approach a professional consultee who is not connected with the conduct of the trial. The researcher will provide information about the trial, as well as the participant information sheet and a covering letter. The consultee will be given adequate time to review the information sheet and an opportunity to ask questions. The consultee will be asked to consider what decision the participant is likely to have made if they had mental capacity. If an initial approach is made to a professional consultee and a personal consultee subsequently becomes available, then the opinion of the personal consultee will be sought. This will override any decision made by the professional consultee. The consultee's opinion regarding the participant's likely views will be recorded on a signed form, counter-signed by the staff member receiving the opinion. This form may be signed physically or electronically, however where neither of these are possible a verbal opinion may be recorded by the staff member and witnessed by one other person.

In rare circumstances, due to time constraints or patients being dishcharged faster than expected, personal/ professional consultee agreement may not be obtained prior to hospital discharge. If this occurs, a researcher at the hospital site from which the patient was discharged will contact the participant's consultee (if it is known that the participant lacks mental capacity) at their home address to seek consent or an opinion. Where possible, the initial contact will be made by post or email to allow time for the patient or consultee to consider their willingness to be contacted. This will be followed by a phone call and second contact if no reply is received. Up to three contact attempts will be made within 28 days of the first contact. The researcher will use available systems to determine correct contact information and, where appropriate, to ensure the participant is still alive.

If the participant or their consultee does not respond to this contact within 28 days of the first contact, then we will assume that they do not agree to collection of further routine data or patient-reported outcome measures. We will include only data collected up to that point in the study analysis.

Patients that do not survive
Following careful consideration and consultation with our PPI advisors, the relatives of those who do not survive to hospital discharge will not be informed of trial participation. It is felt that the burden (further distress) outweighs the benefit (transparency) since the treatments under study are both part of standard clinical practice and are used routinely during IHCA today. Relative-focused information sheets will be developed to enable us to respond to those who may request further information about the trial. This model, developed and agreed with our patient and public advisors, is based on several previous similar large-scale trials that have successfully enrolled cardiac arrest patients. For example, the AIRWAYS-2 trial successfully enrolled more than 9,000 patients using this model without incident or complaint.

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

If the participant regains mental capacity a researcher will approach them at an appropriate time to discuss ongoing study participation. The researcher will provide information about the trial and the participant information sheet. The participant will be given adequate time to review the information sheet and an opportunity to ask questions. The participant's consent to the collection consent form, counter-signed by the staff member taking consent. The consent form may be signed physically, or where the participant is unable to sign the form, either in wet ink or electronically, verbal consent may be recorded by the staff member and witnessed by one other person.

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

Following the cardiac arrest participants may lack mental capacity. Mental capacity will be assessed on an ongoing basis by the patient's clinical team, who will liaise with the local research team to determine the appropriate time to approach the patient and whether a consultee should be approached if the participant is likely to continue to lack mental capacity during their hospital stay.

The general trend is for patients who have suffered a cardiac arrest to improve over time, and regain capacity. If an initial approach is made to a personal or professional consultee and the participant subsequently regains capacity, the participant's consent will be sought. This will override any opinion given by the personal or professional consultee. If a participant who has previously given their consent to continue in the study loses capacity we will continue to collect the primary outcome data from their routine health records (permission for this will be sought as part of the HRA CAG application), but we will not approach them further to complete follow-up questionnaires at 3 and 6 months following the cardiac arrest.

B12-1. What will be the criteria for withdrawal of participants?

If a participant is randomised and later found to be ineligible they will still be included in the trial and analysed under

the principle of “intention to treat”. Similarly, patients who are randomised but do not receive the allocated intervention (for example they achieve a return of spontaneous circulation (ROSC) after randomisation but before advanced airway management is attempted) will be retained and analysed in the group to which they were assigned.

Participants are enrolled without prior consent, and their treatment allocation is completed before there is any opportunity to seek consent or an opinion from a consultee. Therefore, the subsequent approach to survivors seeks their agreement to continue in the study, rather than participate, because they have already done so. Furthermore, allowing survivors to preferentially withdraw risks introducing significant bias to the trial. For this reason, survivors may decline any further participation, but they cannot withdraw from the study entirely, and to maintain the integrity of the trial we are seeking agreement to process a minimum data set (up to the point that consent is sought) and primary outcome data for all enrolled patients without consent. The justification for this is that whilst deceased patients cannot withdraw their data from the study, if those who survive are allowed to withdraw it will create a risk of substantial bias whereby survivors may preferentially withdraw from the study preventing evidence of significant clinical benefit from being detected. In this case we argue that the public interest in completing this research for future patient benefit outweighs the associated breach of confidence.
If at any point following enrolment the patient (or their consultee) indicates that they no longer wish to participate usual care will continue to be provided. This will be logged on the database from the point they cease participation, and no further contact will be made. All non-identifiable data collected up to that point will be retained and included in the analysis.

B12-2. Where a participant is recruited urgently, and later withholds their consent or is withdrawn or dies before consent / consultation can take place, what provisions will apply to the study data collected up to that point?

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, data will continue be collected and submitted to Warwick Clinical Trials Unit. We will obtain approval from the Health Research Authority Confidentiality Advisory Group (CAG) to support the processing of identifiable data without consent. Study data will be linked to data linkage sources for data analysis purposes. Once data linkage has been completed, patient identifiers will be deleted. In the event that the patient survives we plan to routinely collect patient identifiable data to facilitate data linkage otherwise there is a risk of introducing bias in to the study results. Our consent process if focused on the data collection of patient-reported outcomes. Where a participant does not consent to completion of patient reported outcomes (but to the data collection) or we are unable to contact the participant we will continue to collect and process personal identifiable data to facilitate data linkage unless the participant has explicitly withdrawn, or are part of the national opt-out. If they choose to withdraw from the study, we would retain and use anonymised information collected up until that point.

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

At the time of the cardiac arrest, the participant will be unconscious and lack mental capacity to object to the trial intervention. We will therefore approach patients once they regain a capacity (or a consultee if they do not regain capacity prior to hospital discharge) to inform them of the trial and seek their consent to continue in the study with associated options for further data collection.
Patients in hospital after their cardiac arrest will continually be assessed by their clinical team as part of routine care, and any signs of distress will be managed by the clinical team as a component of routine care.

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?

Hospital clinical staff routinely record the resuscitation and treatment preferences of patients, and will manage their care accordingly. Therefore, patients will only be included in the trial if they have expressed a desire to be resuscitated in the event of cardiac arrest; where there is any doubt it is accepted practice to commence resuscitation since it is generally assumed that patients will wish to have the best possible chance of survival.
The national data opt out requires that patients who have previously indicated that they do not wish their data to be used for research are not included in research studies, unless they expressly give their consent to do so. This trial enrols participants without prior consent, and there is also no opportunity to confirm the patient’s national data opt out status prior to enrolment. As a result, we anticipate that we will inadvertently enrol patients who have a national data opt out in place.
Following consultation with our PPI advisors, we propose to withdraw from the study all patients who have registered a national data opt out as soon as possible after enrolment. Only a record of the total number of patients withdrawn from each arm for this reason will be retained to comply with the conventions of CONSORT trial reporting and confirm that the proportion of patients with a national data opt out is the same in the two trial groups. However, we cannot allow patients who have survived to preferentially “opt in” to the trial subsequently, because this may introduce significant bias to the results. Our PPI advisors have therefore recommended that we do not approach survivors who have

registered a national data opt out, since we will have withdrawn them in keeping with their previously expressed wishes, we cannot offer them an option to participate and the burden of this information, when recovering from a life-threatening illness, is of no benefit to the individual.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Matthew Thomas mjcthomas@gmail.com United Kingdom
	Organisation name	UNIVERSITY HOSPITALS BRISTOL AND WESTON NHS FOUNDATION TRUST		
	Address	TRUST HEADQUARTERS MARLBOROUGH STREET BRISTOL		
	Post Code	BS1 3NU		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Stephen Brett stephen.brett@imperial.ac.uk United Kingdom
	Organisation name	IMPERIAL COLLEGE HEALTHCARE NHS TRUST		
	Address	THE BAYS ST MARYS HOSPITAL SOUTH WHARF ROAD LONDON		
	Post Code	W2 1BL		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Jasmeet Soar jasmeetsoar@icloud.com
	Organisation name	NORTH BRISTOL NHS TRUST		
	Address	SOUTHMEAD HOSPITAL SOUTHMEAD ROAD WESTBURY-ON-TRYM BRISTOL		
	Post Code	BS10 5NB		

	Country	ENGLAND	

IN4

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Jerry
		Middle name	Paul
		Family name	Nolan
		Email	Jerry.Nolan@warwick.ac.uk
	Organisation name	ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST	Qualification (MD...)
	Address	COMBE PARK	Country United Kingdom
		BATH	
	Post Code	BA1 3NG	
	Country	ENGLAND	

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Jonathan Benger on 13/07/2022 12:22.

Job Title/Post:	Professor Emergency Care
Organisation:	University of the West of England, Bristol
Email:	Jonathan.Benger@uwe.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Miss Jess Bisset on 15/07/2022 09:14.

Job Title/Post:	Research Projects Manager
Organisation:	University Hospitals Bristol and Weston NHS Foundation Trust
Email:	sarah.bishop3@UHBW.nhs.uk