PROTOCOL

Randomised trial of the clinical and cost effectiveness of a supraglottic airway device versus intubation during in-hospital cardiac arrest (AIRWAYS-3)

ISRCTN Number:	ISRCTN17720457
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Stage:	Final

This protocol has regard for current HRA guidance and content

Protocol Amendments:

Amendment No.	Amendment details	**Date of Amendment**	**Date of Approval**
Substantial Amendment One	Change and clarity to the eligibility criteria to include patients who are currently receiving airways management via a supraglottic airways device upon arrival as this is standard care in many hospitals	18/11/2022	09/12/2022

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SIGNATURE PAGE

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

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

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

For and on behalf of the Study Sponsor:

Signature: Date:
...../.....

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Name (please print):

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Position:
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Chief Investigator:

Signature: Date:
..../.....

Name: (please print):

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TRIAL SUMMARY

Trial Title	Randomised trial of the clinical and cost effectiveness of a supraglottic airway device versus tracheal intubation during in-hospital cardiac arrest (AIRWAYS-3)
Internal ref. number (or short title)	AIRWAYS-3
Trial Design	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) versus tracheal intubation (TI) during in-hospital cardiac arrest (IHCA). The trial will include an internal pilot to confirm feasibility
Trial Participants	Adult (known or believed to be age >=18) hospital inpatients will be eligible for randomisation if they receive resuscitation following IHCA that requires a 2222 call and advanced airway management
Planned sample size	4190 participants
Treatment Duration	Until return of spontaneous circulation (ROSC) for >20 minutes or resuscitation efforts cease, after which the airway will be managed by the attending team as they feel appropriate
Follow-up Duration	6-months post IHCA
Planned Trial Period	1st January 2022 – 31st December 2026
Trial 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 in-hospital cardiac arrest, 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
Primary Outcome Measure	Functional status at hospital discharge (or 30 days post-randomisation whichever is shorter) as measured by the modified Rankin Scale (mRS)
Secondary Outcome Measures	• 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	• Additional unscheduled care and re-admissions (to 6 months) • In-hospital stay utilisation and cost
Safety outcomes	• Adverse event/serious adverse events

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HES	Hospital Episode Statistics
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit & Research Centre
IHCA	In Hospital Cardiac Arrest
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
mRS	Modified Rankin Scale
NCAA	National Cardiac Arrest Audit
PI	Principal Investigator
PPI	Patient & Public Involvement
PWA	Progressive Web App
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
ROSC	Return of Spontaneous Circulation
SAE	Serious Adverse Event
SGA	Supraglottic Airway
SOP	Standard Operating Procedure
TI	Tracheal Intubation
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

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, although the true figure is likely to be higher as the NCAA includes only those patients who are attended by a resuscitation team in response to a 2222 call (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).

During a cardiac arrest, the brain is exposed to critically low oxygen levels, which may result in death or long-term cognitive deficits. Survivors of cardiac arrest who are discharged from hospital commonly describe cognitive impairment. The frequency of this impairment varies because recommended outcome measures report a crude assessment of general neurological function, which often appears good in the majority of cases (2,3). However, in studies using more detailed neuropsychological instruments, cognitive impairment is present in 30-50% of survivors (4,5), and associated with a lower quality of life and increased caregiver strain (5,6).

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.

Research on interventions to improve survival, and the quality of survival, remains highly relevant and important to the needs of the NHS, both now and in the future. The societal impact of cardiac arrest is substantial and evidenced by both the years of productive life lost due to death and disability and the economic burden of caring for cardiac arrest patients who are resuscitated successfully but are left with significant functional impairment (17).

1.2 Existing knowledge

There are very few studies or data sources available to measure IHCA incidence and outcomes, particularly when compared with out of hospital cardiac arrest (OHCA). Observational studies of resuscitation outcomes also tend to be confounded by resuscitation time bias: patients with the best outcomes will be resuscitated (achieve a return of spontaneous circulation) quickly, and before advanced airway management is needed. Therefore, patients who do not require advanced airway management tend to have better outcomes (12,18).

While tracheal intubation (TI) has been considered the definitive technique for advanced airway management during IHCA (7), recent RCTs in out-of-hospital cardiac arrest (OHCA) suggest that there may be advantages to using supraglottic airway (SGA) devices instead of TI as the preferred form of advanced airway management during cardiac arrest (20,21). SGAs are generally quicker and easier to insert (22), and may reduce the frequency and duration of pauses in chest compressions (23).

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 hypoxaemia 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).

A recent (2019) systematic review of advanced airway management during cardiac arrest was conducted to inform the International Liaison Committee of Resuscitation (ILCOR) consensus on CPR science and treatment recommendations, and a member of our team (Soar) authored the review and chaired the process (11). A repeat of these searches (up to 05 January 2021), and a search of the WHO International Clinical Trials Registry Platform for any relevant studies that are planned or in progress identified one further published study (31), and that no relevant trials were being planned or underway. As is the case for cardiac arrest trials in general (12), the ILCOR review found that studies in OHCA far outnumbered studies in IHCA. No controlled trials in the IHCA setting were identified. Only 9 of the 78 observational studies exclusively included IHCA patients and only 3 of these met the review's inclusion criteria. Following its systematic review, ILCOR identified the optimal airway management strategy for IHCA as a significant knowledge gap (11), with additional high-quality studies of airway management in IHCA required as an urgent priority (12).

To understand current practice, and whether there is equipoise in the UK, an online survey and telephone interviews with trainee doctors in anaesthesia and intensive care, identified by the UK Research and Audit Federation of Trainees, was completed to inform this proposal (9). The aims of this research were to: examine current airway management practice during adult IHCA; explore participants' attitudes to potential participation in a randomised trial of airway management during IHCA; explore the feasibility of proposed aspects of trial design; identify potential barriers and facilitators. Completed surveys were received from 128 hospital sites (76% response rate). The majority (96%) of respondents reported immediate access to both TI and SGAs. SGAs were used 'very frequently' or 'frequently' during in-hospital cardiac arrest by 79% of respondents, whilst TI was used 'very frequently' or 'frequently' by 69%. Attitudes towards a randomised trial of airway management strategies during IHCA were highly positive with 80% 'likely' or 'very likely' to participate. As TI and SGA devices are both readily available and used with similar frequency, participants felt there was equipoise in relation to this research question. Randomisation would not cause substantial divergence from usual practice and would therefore be ethically acceptable. These findings have been used to inform and improve our trial design

1.3 Hypothesis

During IHCA, airway management with a SGA is clinically superior and cost-effective when compared with TI.

1.4 Need for a trial

The International Liaison Committee on Resuscitation has highlighted the urgent need for research on airway management during IHCA to improve the quality of care and consequent clinical outcomes.(19) Tracheal intubation skills are limited to relatively few individuals, whereas bag-mask ventilation and the insertion of a SGA can be completed successfully by a wider range of healthcare staff. This has important implications for the composition and function of in-hospital cardiac arrest teams, with an opportunity for improved efficiency.

1.5 Ethical considerations

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).

This trial raises several important ethical issues, which have been considered carefully in the development of this protocol, drawing on the relevant legal and regulatory frameworks and previous experience from successful trials in cardiac arrest, involvement in the Health Research Authority Forum on Consent in Emergency Research, and detailed consultation with patients and the public.

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. However, differential agreement to participate in follow-up arising from early differences in mortality could introduce bias. To avoid this, and ensure 100% data ascertainment of the primary outcome (modified Rankin Scale Score at hospital discharge, or 30 days if the patient remains in hospital at this time), the primary outcome will be collected for all enrolled patients from routinely available data collected by the National Cardiac Arrest Audit with the prior permission of the Health Research Authority Confidentiality Advisory Group (CAG).

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (55).

2. TRIAL DESIGN

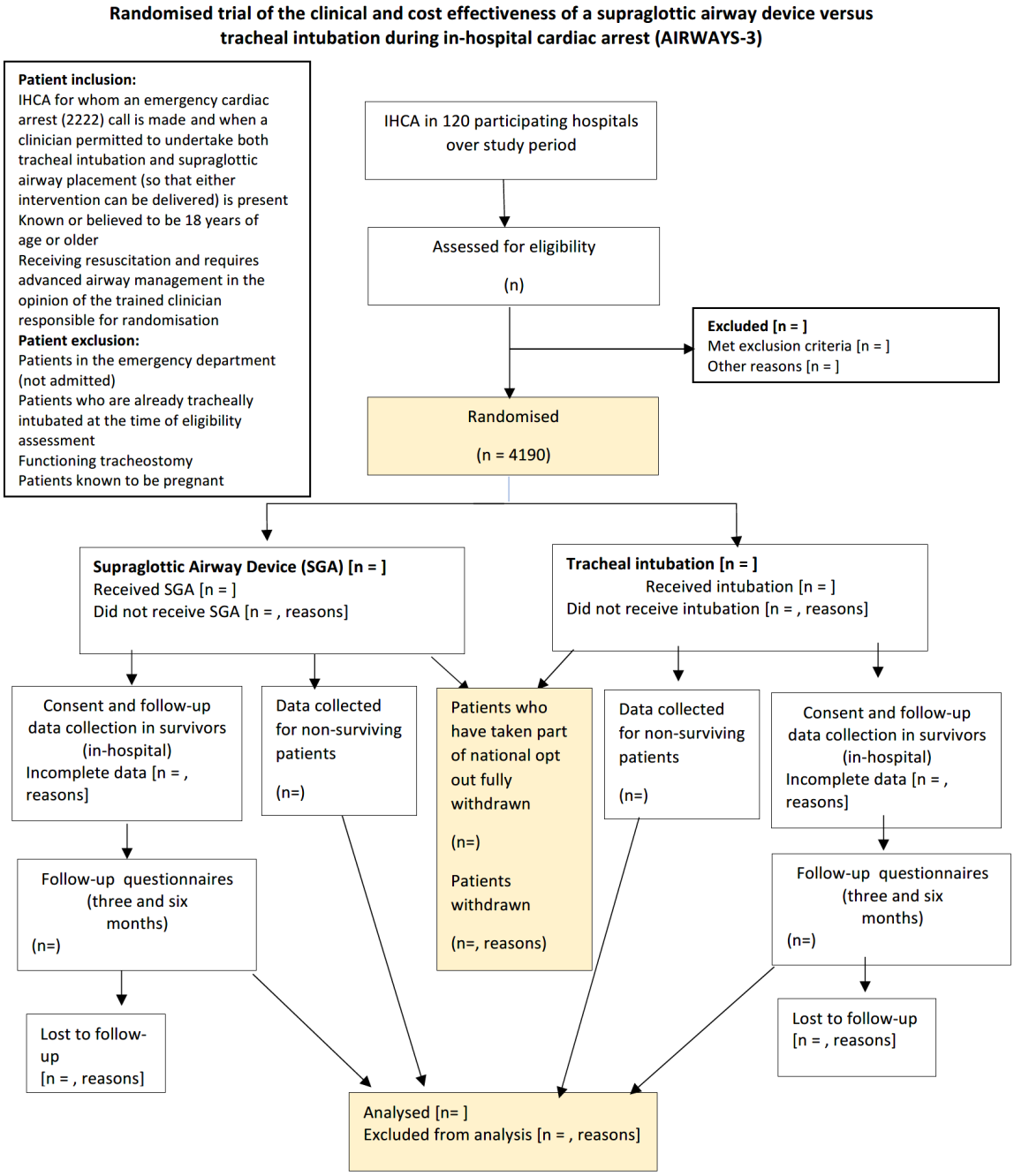
2.1 Trial summary and flow diagram

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 SGA versus TI during IHCA. The trial will be conducted in the acute setting in NHS hospitals throughout the UK.

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.

The primary outcome is the Modified Rankin Scale (mRS) score assessed at hospital discharge or 30 days following IHCA, whichever occurs sooner.

Figure 1 Trial flow diagram



2.2 Aims and objectives

2.2.1 Primary objective

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).

2.2.2 Secondary objective

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

2.3 Outcome measures

The primary outcome for the trial is the modified Rankin Scale score (mRS). This 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 (20,21). A mRS score of 6 indicates that the patient has died.

Functional status at hospital discharge is an outcome that is important to both patients and clinicians. The use of the mRS score over other assessment tools (e.g. cerebral performance category) is recommended in the cardiac arrest core outcome set (41).

Survival to hospital discharge and health-related quality of life are included in the cardiac arrest core outcome set (41), and are therefore included as a secondary outcome measure in this trial.

2.3.1 Efficacy

Primary: Modified Rankin Scale (mRS) score assessed at hospital discharge (or at 30 days post-randomisation if the participant remains in hospital).

Secondary:

- Initial ventilation success (visible chest rise with end tidal carbon dioxide monitoring consistent with successful ventilation (where measured) immediately after insertion of a supraglottic airway device or tracheal tube;
- Regurgitation during the resuscitation attempt (stomach contents seen in the patient's pharynx, mouth or nose), and whether this occurred before, during or after advanced airway management;
- Aspiration during the resuscitation attempt (stomach contents seen below the vocal cords, inside a correctly placed tracheal tube or the airway channel of a correctly placed supraglottic airway device), and whether this occurred before, during or after advanced airway management;
- Return of spontaneous circulation (ROSC) for at least 20 minutes;
- Intensive Care Unit length of stay;
- Hospital length of stay;
- Survival to hospital discharge, 3 and 6 months;
- Functional outcome (mRS) score at 3 and 6 months;

- Health-related quality of life at discharge or 30 days (whichever occurs sooner), 3 and 6 months.

2.3.2 Safety

Adverse events/serious adverse events.

2.3.3 Health Economic

Additional unscheduled care and re-admissions (to 6 months). Resource use will include intervention, hospital (ICU, HDU and ward days) and community costs (primary care and social care costs).

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

- 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 when a clinician permitted to undertake both tracheal intubation and supraglottic airway placement (so that either intervention can be delivered) is present
- Undergoing resuscitation and requiring advanced airway management in the opinion of the trained clinician responsible for randomisation

2.4.2 Exclusion criteria

- Patients in the emergency department
- People who are not a hospital inpatient (e.g. visitor, relative, staff or outpatient)
- Patients who are already tracheally intubated at the time of eligibility assessment
- Patients known to be pregnant
- Patients with a functioning tracheostomy

2.5 Participant identification / Screening

In study hospitals, the cardiac arrest team will be activated by clinical staff via the hospital switchboard as is usual practice. On arrival at the event, the cardiac arrest team will deliver care in accordance with Resuscitation Council UK guidelines. A member of the in-hospital cardiac arrest team who is trained in trial procedures and Good Clinical Practice (GCP), and who has been authorised to enrol patients on the delegation log, will screen the patient to assess their eligibility. This will usually be the member of the in-hospital cardiac arrest team who is designated to manage the patient's airway, however another member of the team may enrol the patient providing they are trained and authorised to do so, and a clinician permitted to undertake both tracheal intubation and supraglottic airway placement is present to manage the patient's airway. 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 (9). This approach will enable study recruitment to be undertaken on a 24/7 basis. Before a clinician permitted to undertake both tracheal intubation and supraglottic airway placement arrives, and randomisation can proceed, the airway will be managed according to usual practice in that hospital site. This will usually be bag-mask ventilation, but may be the temporary placement of a SGA device in some centres.

A record of the event will be made in the study screening log subsequently. If a patient is identified as being eligible, then the patient will proceed to randomisation.

2.6 Site Staff Training

Educational and training materials will be developed to standardise the processes for training in study procedures, trial enrolment, treatment delivery, data recording and proportionate GCP. Materials will be developed to support study staff at the site initiation visit, which may be conducted virtually. In addition to this, the AIRWAYS-3 trial team will: provide advice and support to site PIs; provide instructional material to all trial sites; provide detailed instructions on protocol and a training manual which may be delivered in video and online formats.

2.7 Consent Procedures

2.7.1 Research Without Prior Consent and the Health Research Authority Framework

The time-critical nature of the emergency and patient status (immediately unconscious due to cardiac arrest) means it will not be feasible to seek informed consent from the patient or a consultee before trial enrolment. The trial will fall under the legislative framework of the Mental Capacity Act 2005. Approval from an appropriately "flagged" research ethics committee to enrol patients without prior consent will be sought. This approach is permitted under the Mental Capacity Act 2005 for life-threatening conditions such as cardiac arrest where there is no practical alternative. This protocol has been prepared for recruitment in England and Wales, in consideration of the legal requirements in these nations. Should recruitment occur in Scotland or Northern Ireland it will be updated accordingly, taking account of the differences in legislation that exist in the devolved nations.

2.7.2 Participants who survive

For patients who survive, the hospital research team will provide trial information and seek patient consent for ongoing participation. In the event the patient lacks capacity an appropriate personal or professional consultee will be approached instead. A personal consultee is preferred, and a professional consultee will only be approached if no personal consultee can be identified before the patient is discharged from hospital, or a potential personal consultee declines to take on this role. NHS interpreter services will be used, as and when required, to support the provision of information to participants. Experience in previous trials is that this approach is well received by patients and families who appreciate the research team taking the time to explain the trial to them, and this has led to high levels of consent to continue. However, to ensure 100% ascertainment of the primary outcome this will be collected for all enrolled patients (those who do and do not survive) from routinely available data collected by the National Cardiac Arrest Audit with the prior permission of the Health Research Authority Confidentiality Advisory Group (CAG).

When an approach is made, the trial intervention will have been completed. The researcher will inform the participant (or their consultee) of their enrolment and explain that the focus of the consent process relates to ongoing participation; namely the collection of routinely available data and patient-reported outcome measures through questionnaires. 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. This is considered further in Section 7.3 (Confidentiality Advisory Group (CAG) approval).

2.7.3 Participants with mental capacity

If the participant regains mental capacity a researcher will approach them at an appropriate time, working in close liaison with the clinical staff who are caring for the patient, 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. This may require several discussions over a period of time. The participant's consent to the collection of routine data and patient-reported outcome measures will be recorded on a signed 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. Electronic consent will be taken through Qualtrics to ensure a clear audit trail and security.

2.7.3.1 Participants who lack mental capacity

Participants may lack capacity following the cardiac arrest. This may be temporary or permanent.

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 cover 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, or a potential personal consultee is unwilling to take on this role, 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 part in which 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 on the collection of routine data and patient-reported outcome measures will be recorded on a signed form, counter-signed by the staff member receiving the opinion. This form may be signed physically or electronically as described above, however where 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 prior to hospital discharge, then 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. If they regain capacity subsequently, we will seek their consent to continue in the study and proceed according to their wishes.

2.7.3.2 **Approaching patients or their consultee following discharge**

In rare circumstances, participant consent or a personal/ professional consultee opinion may not be obtained before hospital discharge.

If this occurs, a researcher at the hospital site from which the patient was discharged will contact the participant or their 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. Where available, more than one system will be accessed to determine survival status.

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.

2.7.4 Patients who do not survive

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. 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 both inside and outside hospital.

2.8 Randomisation

2.8.1 Randomisation

The randomisation algorithm will be provided by Warwick Clinical Trials Unit (WCTU). A computer-generated randomisation sequence will be created, stratified by hospital site and time of day (8am to 6pm or outside of these hours). Time of day is included as a stratification variable because out-of-hours cardiac arrests tend to have less favourable outcomes (42). Patients will be randomised 1:1 to SGA or TI. Randomisation will take place using a bespoke mobile phone progressive web application (PWA), which will be developed by the programming team at WCTU. The PWA will function 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 for 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.

2.8.2 Post-randomisation withdrawals, exclusions and moves out of region

Post randomisation exclusions may be authorised by the trial management group and approved by the Trial Steering Committee if a participant is randomised in error. However, 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. In making any decision to exclude after randomisation care will be taken to avoid introducing bias (42).

Participants may cease trial follow-up at any time without prejudice. Unless a participant who has previously consented to continuing data collection explicitly ceases their participation, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

If at any point following consent 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. If the patient (or their consultee) indicates that they wish to be withdrawn from the study, no further data will be collected and no further contact will be made. All non-identifiable data collected prior to consent and the primary outcome will be retained and included in the analysis.

2.9 Trial treatments / intervention

2.9.1 Trial treatment(s) / intervention

Intervention: A **supraglottic airway device** of the type used routinely in that hospital. 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. If a functioning SGA has already been placed at the point of randomisation, and the patient is randomised to SGA, this device may be left in situ. Two attempts at SGA placement should be made. An attempt is defined as introducing a SGA past the teeth, and concludes when the SGA is removed from the mouth. If two attempts at SGA placement are 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.

Comparator: **Tracheal intubation.** During resuscitation tracheal intubation should occur, with end-tidal carbon dioxide monitoring wherever possible, following an initial period of bag-mask ventilation as required. If a functioning SGA has already been placed at the point of randomisation, and the patient is randomised to tracheal intubation, the SGA should be removed and tracheal intubation attempted. Two attempts at intubation should be made. An attempt is defined as introducing the laryngoscope past the teeth, and concludes when the laryngoscope is removed from the mouth,

regardless of whether or not a tracheal tube is inserted. If two attempts at tracheal intubation are 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.

2.9.2 Compliance/contamination

Treatment fidelity will be closely monitored and assessed throughout the pilot study. We will obtain feedback from sites and enhance all processes to ensure that the delivery of both interventions is as protocolised as possible. A set of standardised training materials will be developed to meet the needs of all staff involved in the trial. In the event of evidence of non-compliance, this will be flagged to the site research team. The site research team will then investigate events through discussion with the clinical team and, where appropriate, will report this as a non-compliance. Where necessary, further training and support will be provided.

Contamination due to crossover: crossovers will lead to contamination of the initial randomised intervention due to a mixing of effects in the outcomes, reducing the power of the study. This is further complicated by the fact that crossover may be a selective process whereby patients who have their treatment switched have a different prognosis compared with those who do not. Crossover will be monitored and training provided to sites to trouble-shoot issues related to crossover where necessary. The impact of crossover on the statistical power of the trial is discussed further in the statistical analysis section (section 6.0).

2.10 Methods to minimise bias

2.10.1 Concealment and blinding

Treatment allocation will be concealed prior to randomisation using a bespoke, computerised randomisation PWA. Screening logs will be assessed to examine reasons why patients have not been enrolled into the study.

The majority of outcomes are objective and will not be influenced by knowledge of treatment allocation. It will not be possible to blind clinical team members to treatment allocation following randomisation. Blinding of the wider clinical team and site research team will be limited as cardiac arrest team members may document treatment allocation in the patient's medical record. Patients will be blinded because they are in cardiac arrest and unconscious when the allocated airway management occurs. Site teams will be encouraged to maintain blinding by not informing patients or their relatives of their treatment allocation, unless the participant or consultee states a specific wish to be informed.

2.10.2 Unblinding

There is no requirement for unblinding procedures due to the open-label nature of the trial.

2.11 Co-enrolment into other trials

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 and supported by co-enrolment agreements.

2.12 End of trial

The trial will end when all participants have completed their 6-month follow-up, or receipt of routinely collected data, whichever is later.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC) and/or Trial Steering Committee (TSC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days in the event of early termination of all trial related activities.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 1 describes the trial assessments and timepoints for data collection.

Table 1 Trial assessments

Visit	**1**	**2**	**3**	**4**
Visit Window (No. Weeks ± No. Days)	**Baseline**	**Hospital Discharge (or 30 days post randomisation)**	**3 calendar months (±4 weeks) After V 1**	**6 calendar months (± 4 weeks) After V 2**
Informed consent		✓*		
Inclusion/exclusion criteria	✓			
Randomisation	✓			
Intervention	✓			
Modified Rankin Scale score		✓	✓	✓
Quality of Life (EQ-5D-5L)		✓	✓	✓
Adverse events	✓	✓	✓	✓
Resource utilisation				✓
Other				

*Once participants have recovered sufficiently (usually around the time of discharge from the Intensive Care Unit) and whilst they are still in hospital, a member of the hospital research team will approach the patient (or if they lack capacity a consultee) to explain the study and seek consent to continue in the trial

3.2 Data Collection

3.2.1 Participant enrolment

The randomisation PWA will collect anonymised data relating to the management and initial outcome of the cardiac arrest call. The NCAA (a national clinical audit of in-hospital cardiac arrests in the UK) will provide data on patient and cardiac arrest characteristics.

3.2.2 Hospital follow-up

The NCAA will provide data on 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.

3.2.3 Long term follow-up assessments

Consistent with the core outcome set recommendations, health related quality of life will be measured using EQ-5D-5L at discharge/30 days, 3 and 6 months. mRS will also be measured at 3 and 6 months. The EQ-5D-5L captures the timespan over which functional/neurological recovery tends to plateau (43). It is less burdensome to complete than other tools, is freely available, accessible in multiple languages and may be completed by the patient or a proxy. It comprises five dimensions: mobility; self-care; usual activities; pain/discomfort; anxiety/depression. Each dimension has 5 levels: no problems; slight problems; moderate problems; severe problems; extreme problems. From the EQ-5D-5L health utilities will be calculated for all participants, using standard tariffs. A £15 voucher will be given to every participant who completes a questionnaire at 3 months, and again at 6 months, to acknowledge their contribution to the study.

Longer-term follow up: data will be obtained from NHS Digital Hospital Episode Statistics (for further Emergency Department attendances and hospital admissions up to 6 months post randomisation), the National Cardiac Arrest Audit (for mRS at discharge or 30 days and length of hospital stay) and the Case Mix Programme National Clinical Audit for adult intensive care (for length of ITU stay) to enable efficient, long-term follow-up of patients. 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 to ensure effective follow up (rates > 98% in previous studies) (34,35).

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant *participating in a clinical study* and which does not necessarily have a causal relationship with the treatment/intervention.

4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Immediate intervention was required to prevent one of the above or is an important medical condition.

4.2 Assessing and reporting AEs, SAEs, ADEs, SADEs and related SAEs

The assessment and reporting of AEs, SAEs and related SAEs will follow the relevant Warwick CTU SOPs. This trial is comparing two interventions that are already in routine use in NHS clinical practice and which will be used in accordance with manufacturer's instructions.

All patients in this trial will be in an immediately life-threatening situation; many will not survive, and all of those who do will be hospitalised, with the majority of survivors admitted to intensive care. These situations are therefore anticipated as a result of the condition, and events leading to any of them should only be reported as an SAE if their cause was clearly separate from the cardiac arrest. Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation (including death and intensive care admission) should not be reported. Clinical details about these events will be routinely collected in the case report form as part of the trial outcomes.

Events should be reported as a serious adverse event only if they:

- occur between randomisation and hospital discharge
- are serious AND are potentially related to trial participation, i.e. may have resulted from study treatment such as use of a SGA or TI;

AND

- are unexpected, i.e. the event is not an expected occurrence for patients who have had a cardiac arrest and received advanced airway management.

Examples of events that should not be reported as SAEs because they are anticipated following IHCA:

- death
- brain injury
- ITU admission
- aspiration pneumonia

Examples of events that may be SAEs are;

- use of one of the interventions causing a new injury that endangers the patient,
- unrecognised oesophageal intubation,

Adverse events should be recorded on the case report form. Events that meet criteria for seriousness should be reported to WCTU Quality Assurance Team and the sponsor within 24-hours of becoming aware of the event.

Once an adverse event or serious adverse event has been identified, the participant should continue to be followed-up until resolution of the event or a final outcome has been reached. Following reporting of a serious adverse event, any change of condition or other follow-up

information should be sent to the WCTU Quality Assurance team and sponsor as soon as is practicably possible

The trial manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. All other recruiting sites in the trial will be informed of the event and any implications for the trial.

The causality of SAEs (i.e. relationship to trial intervention- see table) will be assessed by the investigator(s) on the SAE form (see table).

Relationship to trial intervention	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

All SAE reports will be reviewed on receipt by the Chief Investigator (or their delegate) for an independent causality assessment and those that are considered to satisfy the criteria for being possibly related, probably related or definitely related to trial interventions (either by the PI or CI) and which are not exempt from reporting will be assessed for expectedness by the CI or a clinical delegate. SAEs that are deemed to be unexpected and related to the intervention will be notified to the REC and sponsor within 15 days of receipt in accordance with regulatory requirements. All such events will be reported to the Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings. Reports of all SAEs by randomisation arm will also be reviewed by the DMC at their regular meetings, or more frequently if requested by the DMC Chair.

Adverse Device Events and Serious Adverse Device Events

In the event of problems with a device in use we will notify the MHRA in accordance with WCTU SOP 17, part 2.

Examples of ADEs and SADEs include:

- malfunction of the device causing injury to the clinical team,
- malfunction of the device leading to inadequate patient ventilation.

4.3 Responsibilities

Principal Investigator (PI):

Checking for AEs when participants are reviewed or followed-up.

1. Using medical judgement in assigning seriousness and causality
2. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning causality
3. Immediate review of all related and unexpected SAEs
4. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Production and submission of annual reports to the relevant REC.

Sponsor or delegate:

1. Central data collection and verification of AEs, and SAEs, according to the trial protocol.
2. Expectedness assessment of related SAEs
3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
6. Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee (TSC):

In accordance with the Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.4 Notification of deaths

Death is collected as a study outcome. No separate notification of death is required.

4.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with UK GDPR and Warwick SOPs. Due to the need to link data across datasets, approval to hold confidential data without consent will be sought from the Health Research Authority Confidentiality Advisory Group (CAG).

Personal identifiable data will be held separately to trial data on the trial database, with linkage provided through a unique trial 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.

5.1 Data collection and management

Data management processes will be documented in a Data Management Plan. Case Report Forms (CRFs) entered directly on to the database and a Progressive Web Application (PWA) will be developed to collect all required trial data. Where applicable, a random sample of at least 10% of CRFs will be checked, by the study Research Team, against entries within the database and the source data for quality purposes. The percentage checked will be increased if a significant error rate is found. In addition, the first set of recruitment data collected from all new sites will be scrutinized.

Hospital admission through to discharge: The PWA will collect data at randomisation, including data related to the management and initial outcome of the cardiac arrest call. The National Cardiac Arrest Audit (NCAA) is a national clinical audit of in-hospital cardiac arrests in the UK. The NCAA database will be used to collect 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. Identifiable data will be collected on a CRF by the hospital clinical and research team for data linkage purposes.

Post discharge and long term follow-up (3 and 6 months): Consistent with the core outcome set recommendations, modified Rankin Scale and health related quality of life using EQ-5D-5L will be measured at 3 and 6 months. Following confirmation of survival status, participants will be followed up at 3 and 6 months and asked to complete these two questionnaires. The patient may opt to complete these questionnaires by post, online or by telephone according to their preferences, and will be given a £15 voucher at each time point to acknowledge their contribution. If the participant lacks capacity then a consultee may complete the questionnaires on their behalf. If the participant or

consultee cannot be reached after 3 contact attempts no further attempts will be made on that occasion, however if they do not respond after 3 contact attempts at 3 months a further contact will be made (on up to 3 occasions) at 6 months.

Longer-term follow up: Data will be obtained from NHS Digital Hospital Episode Statistics, the National Cardiac Arrest Audit (NCAA) and the Case Mix Programme National Clinical Audit to enable efficient, long-term follow-up of patients. Data sharing agreements will be in place for each organisation involved in data linkage to cover the sharing of personal data. 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 legal representatives to ensure effective follow up.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU and recruiting sites in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All essential documents, including patient records and other source documents will be retained for a period of 10 years following the end of the study. Where study related information is documented in the hard copy medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 5 years after the last patient last visit. Where electronic records are in use, trust policy will be followed.

5.4 Data access and quality assurance

All data access will be controlled by individual usernames and passwords and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role and responsibilities in the study documented on the central coordinating delegation log. Any data that are transferred out of the secure environment (for example for statistical analysis) will adhere to Warwick SOPs.

5.5 Data Shared with Third Parties

The trial statisticians and DMC will have access to the dataset for the analysis of trial outcomes. Once the main analyses have been undertaken, de-identified individual participant data will be available to other investigators subject to approval of data analysis plans and compliance with the University of Warwick SOPs on Data Management and Sharing. Approval of data analysis plans will be the responsibility of the TSC during the lifetime of the trial. Following study completion, the Chief Investigator and WCTU Data Sharing Committee will be jointly responsible for the approval of data analysis plans. The trial will comply with Data Sharing Policies that may be instituted by the NIHR during the lifetime of the project.

5.6 Archiving

Trial documentation and data held at Warwick Clinical Trials Unit that is required for reconstruction of the study results will be archived for at least 10 years from the close of the study. The trial master

file and associated data will be archived by WCTU. All personal data for which there is no longer a purpose to hold will be removed at the point at which it is no longer required. An anonymised data set will be held indefinitely after the 10 year period, to allow for data sharing and maximise benefit. This will be included in the participant information sheet and consent form.

The local Principal Investigators will maintain all records and documents regarding the conduct of the study. Where study related information is documented in the hard copy medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 5 years after the last patient last visit. Where electronic records are in use, trust policy will be followed. 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.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

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%).

6.2 Statistical analysis of efficacy and harms

6.2.1 Statistics and data analysis

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 pre-defined important fixed covariates. These covariates will be included in the analysis plan, prior to any analysis. Secondary outcomes which are categorical will be analysed in a similar way (using mixed-effects logistic regression models). For continuous outcomes, we will assess the distribution of the data and use appropriate analytical methods – if the data is normally distributed we will use mixed-effects linear regression models and

if it is non-normal we will use log transform of the data or the gamma distribution to model the data. 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 weighted (IPW) analysis to account for crossovers, using the primary outcome measure.

INTERNAL PILOT

The main trial will be preceded by an internal pilot study of 6 months duration. This will follow the same processes as the main trial, and all patients recruited to the pilot study will be included in the final analysis. The pilot will take place in 40 representative sites to confirm recruitment rates, protocol compliance and data collection, and will aim to recruit 420 patients representing 10% of the total study sample.(36) In particular, we will audit: (a) screening data; (b) recruitment; (c) reasons for exclusion; (d) protocol adherence, crossovers and fidelity to the intervention; (e) implementation of the training and protocol into practice, using screening logs, case report forms (CRFs) and virtual site visits. We will also review the assumptions on which the sample size calculation is based.

The recruitment rate during the pilot study is shown in the recruitment section.

Trial progression criteria will be:

	Red	Amber	Green
RECRUITMENT			
% Threshold	<60%	60-99%	100%
Sites recruited	<25	26-39	40
Total number of participants recruited	<252	252-419	420
COMPLIANCE/ADHERENCE (of those recruited)			
% Threshold	<75%	75-85%	86-100%
Total number of participants compliant	<180	180-305	306-420

Success criteria for recruitment will be (a) 100% recruitment: progress to main trial; (b) 60-99% recruitment: progress to main trial with review of screening log and protocol, adjustments to the protocol and research processes as required and explore the possibility of additional sites; (c) less than 60% recruitment: progression to main trial not anticipated.

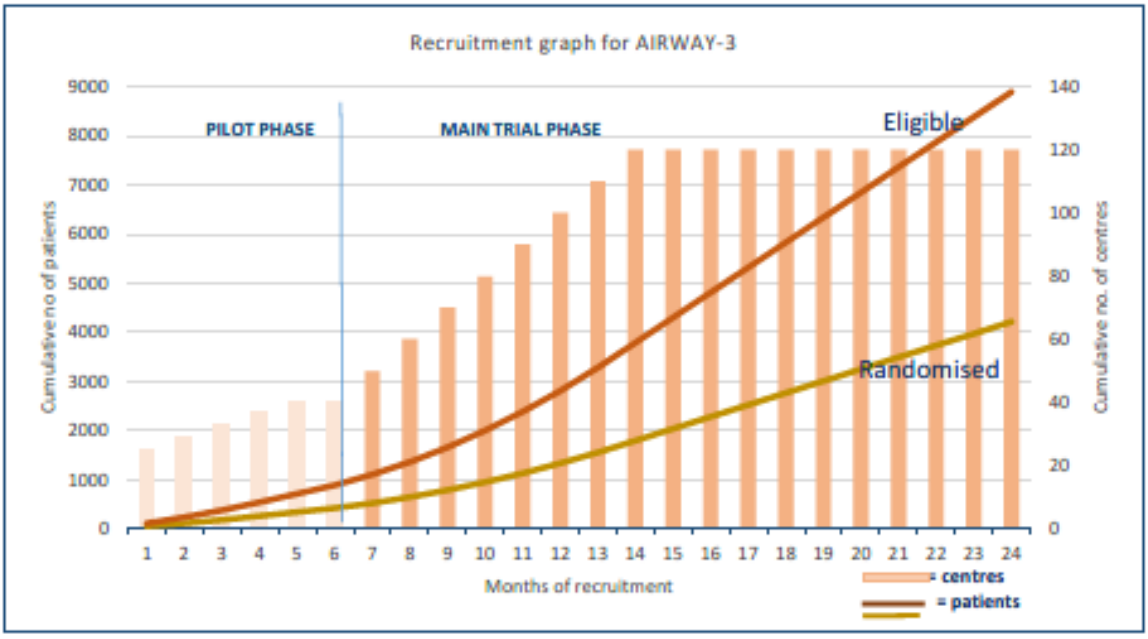
Success criteria for protocol adherence and fidelity to the intervention: (a) 86-100% adherence: progress to main trial; (b) 75-85% adherence: progress to main trial with intensive efforts to improve adherence informed by learning from pilot sites; (c) < 75% adherence: progression to main trial not anticipated.

These criteria will be reviewed by the Data Monitoring and Ethics Committee (DMC) and the Trial Steering Committee (TSC) in association with the HTA secretariat.

On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial. The pilot study results will be reported in the HTA Monograph in accordance with the CONSORT guideline for pilot studies (37).

6.2.2 Planned recruitment rate

Recruitment has been based on the COMPRESS study (personal correspondence), which was a feasibility study comparing "hands-on" chest compressions with an automated external compressions device during adult in-hospital cardiac arrest, carried out by one of the co-applicant team (Couper) at the Warwick CTU. The clinical population for AIRWAYS-3 is very similar to that included in the COMPRESS study. In COMPRESS, which was more challenging to recruit to than this trial and did not recruit 24/7, the number of eligible patients was 2.1 times those randomised. In relation to these figures, and our sample size calculation, it is expected that 14,000 patients will be screened during the trial, of which 8,400 are expected to be eligible for AIRWAYS-3 and of those 4,200 (50%) will be recruited.



6.2.3.2 Primary outcome analysis

The mRS is a 7-point scale which measures the functional outcome of patients. The scaling is as follows: 0 - No symptoms; 1 - No significant disability- able to carry out all usual activities, despite some symptoms; 2 - Slight disability –able to look after own affairs without assistance, but unable to carry out all previous activities; 3 - Moderate disability- requires some help, but able to walk unassisted; 4 – Moderately severe disability - unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5 - Severe disability - requires constant nursing care and attention, bedridden, incontinent; 6 – Dead

6.2.3.3 Secondary outcome analysis

Outcome	Source of Data	Justification
Initial ventilation success (visible chest rise and evidence of end	*App data entry following IHCA*	*Primary goal of advanced airway management is to deliver effective ventilation*

tidal carbon dioxide on capnography)		
Regurgitation (stomach contents visible in the mouth or nose) or aspiration (stomach contents visible below the vocal cords or inside a correctly placed tracheal tube or airway channel of a supraglottic airway device)	*App data entry following IHCA*	*Different advanced airway management techniques may be associated with different risks of regurgitation and/or aspiration*
Return of spontaneous circulation (ROSC) > 20 minutes	*NCAA*	*Short-term outcome following cardiac arrest*
Critical care length of stay (number of days from randomisation	*NCAA, HES*	*Measure of health service use, Required for health economic analysis*
Hospital length of stay (number of days from randomisation)	*NCAA, HES*	*Measure of health service use, Required for health economic analysis*
Survival to hospital discharge, 3-months and 6-months	*NCAA, HES*	*Included in the cardiac arrest core outcome set*
mRS score at 3-months and 6-months	*Postal CRF/eCRF/CRF completed by telephone*	*Included in the cardiac arrest core outcome set; patient-centred outcome*
Health-related quality of life (EQ-5D-5L) at 3-months and 6-months	*Postal CRF/eCRF/CRF completed by telephone*	*Included in the cardiac arrest core outcome set; required for health economic analysis; patient-centred outcome*
In-hospital stay utilization and costs	*HES*	*Required for health economic analysis*
Additional unscheduled care and readmission (to 6 months)	*HES*	*Required for health economic analysis*
Adverse events/ serious adverse events	*CRF (in-hospital patient notes)*	*All serious adverse events and adverse events that are related to the intervention will be reported, in line with Warwick CTU operating procedures.*

6.3 Subgroup analyses

Sub-group analyses will include the assessment of treatment allocation, shockable/non-shockable initial rhythm and the presumed cause of the cardiac arrest. This pre-specified exploratory subgroup analysis will be analysed using interaction terms (treatment x sub-group) in the statistical models and reported using 95% confidence intervals, as the trial is not powered to identify interactions.

6.4 Interim analysis and criteria for the premature termination of the trial

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.

6.5 Patient population

Patients can be enrolled sequentially by clinical members of the cardiac arrest response team on a 24/7 basis. Recruitment will be carefully monitored using screening logs based on hospital emergency cardiac arrest call logs and data returned routinely to the National Cardiac Arrest Audit (NCAA) to ensure as many eligible patients are randomised as possible.

The broad inclusion/exclusion criteria will ensure that the trial findings are generalizable to the UK in-hospital adult cardiac arrest population. This will maximize the opportunity for IHCA patients to participate in this research. Children are excluded because: i) the aetiology of cardiac arrest in children is more commonly due to a respiratory pathology such that tracheal intubation is more frequently used in this group and there is unlikely to be equipoise to randomise to a supraglottic airway; ii) differences in anatomy increase the complexity of airway management in children; iii) functional assessment measures in children are different to those used in adults such that it would not be possible to combine outcomes across children and adult groups. Emergency department cardiac arrests are excluded as these events will include patients that sustain a cardiac arrest outside hospital and who have been transferred to the hospital whilst cardiac arrest and resuscitation are ongoing. This is a different patient population to which other evidence and randomised trials apply (20,21). Similarly, individuals who are not hospital inpatients will more closely resemble out of hospital cardiac arrest patients. In pregnancy, and particularly later pregnancy, tracheal intubation is generally preferred due to the increased risk of regurgitation and aspiration and the potential need to generate higher airway pressures; this means that equipoise does not exist in this patient group. Patients already receiving advanced airway management are excluded since it would be clinically inappropriate to remove a functioning advanced airway device as a result of study enrolment. Patients with a functioning tracheostomy are rare and require a specialist approach to airway management that is outside the scope of this trial.

6.6 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective using NICE Reference Case approach (47). Resource use will include intervention, hospital (ICU, HDU and ward days) and community costs (primary care and social care costs) in the 6 months following randomisation. Resources will be costed using national reference unit costs where available, reflated to current prices. A secondary societal perspective will additionally include time lost from work (paid/unpaid) and patient borne health costs (e.g. wheelchair by type, home adaptations, feeding aids, walking aids, home-help, support from relatives). Health-related quality of life (EQ-5D-5L) responses will be used to generate quality-adjusted life years (QALYs) using the valuations recommended by NICE and using the area-under-the curve (AUC) method.(48,49) Baseline EQ-5D-5L values will be set to reflect the unconscious health state minimising potential bias in the

QALY AUC calculation.(50,51) Within-trial analysis (to 6 months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost-effectiveness. Missingness mechanisms will be explored and multiple imputation methods used where appropriate to avoid biases associated with complete case analysis (52-54). Within-trial findings, reflecting the outcomes and prognosis of patients at 6 months, will inform a lifetime decision-analytic model. Modelling will draw upon best available information from the literature to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer term costs and consequences will be discounted to present values at 3.5% per annum. Sensitivity analyses will be undertaken to explore uncertainty and to consider issues of generalisability of the study. Presentation of findings for the within-trial analysis and model will include incremental cost-effectiveness ratio planes, incremental net monetary benefit, cost-effectiveness acceptability curves and value of information.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The trial will be sponsored by University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). UHBW has substantial experience of the oversight of NIHR-funded clinical trials in the NHS. All trial-related activity will be undertaken according to the principles set out in the Good Clinical Practice Guidance and in accordance with the UK Policy Framework for Health and Social Care Research.

The study will be performed subject to favourable opinion/ authorisation/permission or equivalent from all necessary regulatory and other bodies. This includes but is not limited to REC, HRA, NHS Trusts.

7.2 Ethics approval

Ethics committee review of the trial protocol and documents essential to the trial will be carried out by a UK NHS research ethics committee, flagged for studies involving adults lacking capacity. The required ethical approval for the trial will be sought using the Integrated Research Application System (IRAS). HRA approval will be obtained before the study starts, and when all other approvals are in place. Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has been reviewed by the relevant NHS Trust Research & Development (R&D) department.

Sites will not be permitted to enrol patients into the trial until written confirmation of the approval via the HRA is received by the AIRWAYS-3 trial team, based at WCTU. As the trial will recruit participants without prior consent in accordance with the Mental Capacity Act 2005, approval will also be sought from the Health Research Authority Confidentiality Advisory Group (CAG) to support the processing of confidential data without consent.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and HRA will be notified of any amendments, and once the trial concludes a final report will be provided in accordance with reporting requirements. In accordance to Warwick SOPs, the CI is responsible for making applications to the relevant authorities if an amendment to the research protocol or other study document or process is required. The CI may designate a member of staff to prepare the amendment submission but retains responsibility for any amendment application, however, the CI is no longer required to sign the completed amendment tool but should be copied into any correspondence with the relevant sponsors' office. It is the sponsor's responsibility to assess whether an amendment is

to be regarded as 'substantial' on a case-by-case basis and confirm their opinion with the CI or their delegate prior to any application being made. The sponsor is required to review and sign off the amendment tool prior to locking for submission. This will be returned to WCTU for submission and processing of the amendment. The WCTU study management team will ensure that an impact assessment is carried out on all key study documents (e.g. protocol, CRFs, data management plan, SAP, Risk Assessment and Monitoring Plan) to check if any associated documents require amending based on the proposed amendments to the study.

As part of the funding decision by the NIHR HTA, the trial has been reviewed by both the HTA board and independent individuals with clinical, methodological, and patient involvement expertise. It is a requirement to send to the NIHR any substantial protocol amendment documents for their approval prior to submission to the main REC.

7.3 Confidentiality Advisory Group (CAG) approval

An application will be made to CAG to process confidential patient information without individual patient consent. There are several elements that will need to be considered and carefully described in the CAG application:

7.3.1 Access to a deceased person's data

The majority of patients enrolled in the trial will die before regaining capacity. It is clearly not feasible to obtain consent from a person who is deceased. 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 will apply to CAG to process a defined data set for deceased persons for the minimum time required to complete data analysis, after which the data set will be anonymised and all confidential patient information will be destroyed. This is particularly important to ensure 100% ascertainment of the primary outcome and is one of CAG's "precedent set categories" which have been developed to enable a more timely review process.

7.3.2 Collection of primary outcome data

Because there is no practical alternative, patient enrolment will take place without prior consent. We will therefore approach patients once they regain a capacity (or a consultee if they do not regain capacity following transfer to a general hospital ward) to inform them of the trial and seek their consent to continue in the study with associated options for further data collection. However, the patient cannot decline to participate in the trial since they have already been randomised and received the trial intervention. We will seek the agreement of CAG to process all data collected up to the point that a participant is approached for consent, and also the primary outcome for all enrolled patients, without their 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.

7.3.3 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 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 additional burden of this information, when recovering from a life-threatening illness, is of no benefit to the individual. We will be informing any patients who have opted out of any SAE occurrence.

7.4 Trial Registration

The AIRWAYS-3 trial will be registered with the International Standard Registered Clinical/soCial sTudy Number (ISRCTN) Register.

7.5 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

7.6 Indemnity

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.

7.7 Trial timetable and milestones

PROJECT ACTIVITY (RANGE OF MONTHS)	1 TO 9	10 TO 15	16 TO 21	22 TO 27	28 TO 33	34 TO 38	39 TO 40	41 TO 42	43 TO 48
PROJECT ACTIVITY (48 MONTHS)	9	6	6	6	6	6	2	1	6
STAGE OF TRIAL	*set-up*	*pilot*	*main trial*	*main trial*	*main trial*	*follow-up*	*follow-up*	*analysis*	*reporting*
site set-up									
training initiated									
Ethincs regulatory approvals									
Final protocol/draft CRFs									
Set up processes for NCAA data									
START OF PILOT									
sites open		**40**							
patient recruitment		*							
3 month follow-up		*							
6 month follow-up		*							
MAIN TRIAL									
sites open (cumulative)			**100**	**120**	**120**				
patient recruitment			*	*	*				
3 month follow-up				*	*	*	*		
6 month follow-up				*	*	*	*		
TRIAL MANAGEMENT/REPORTING									
data processing	Prep								
data analysis	prep								
TMG meetings	*****	*****	*****	*****	*****	*****	*****	*****	
TSC meetings	*	*	*	*	*	*			
DMeC meetings	*	*	*	*	*	*			*
PPI Panel meetings	***	***	***	***	***	***		***	***
Monitoring report	*	*	*	*	*	*		*	*
Dissemination	*	*	*	*	*	*		*	*
Eligible patients (x 2.1 of randomised)		886	2811	5832	8896				
Patient accrual		420	840	1260	1680				
Patient accrual (cumulative)		**420**	**1332**	**2764**	**4216**				

7.8 Administration

The study will be coordinated by the Warwick CTU (WCTU) which has specific expertise in undertaking studies in emergency and critical care. The study will be conducted according to defined Warwick SOPs.

The WCTU will be responsible for protocol development, ethics and governance approvals, database development and data management, randomisation, trial management and monitoring, analysis of the data and reporting.

The study will be monitored in accordance with Warwick CTU's Monitoring SOP. All study related documents will be made available on request for monitoring and audit by Warwick CTU, the Sponsor, the relevant Research Ethics Committee and for any other regulatory authorities.

7.9 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff, co-investigators and patient and public representation involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

7.10 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as two 'lay' representatives. The TSC will have an independent Chairperson. Meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or videoconferencing.

The Steering Committee, in the development of this protocol and throughout the trial, will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.11 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet after the first 10% of patients have been recruited or after 9 months recruitment, whichever is sooner, and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

DMC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.12 Essential Documentation

A Trial Master File will be set up according to the appropriate Warwick SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7.13 Financial Support

The trial is funded by the National Institute for Health Research (NIHR) HTA programme reference NIHR131533. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

8. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed 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.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

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. 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 similar cardiac arrest studies. The involvement of these contributors will be key in carrying this trial through to completion.

Two PPI representatives will join the independent trial steering committee as full members, and regular reports will be provided to all our patient and public contributors throughout the study, seeking the benefit of their experience and advice as the research proceeds. It is anticipated that the core Patient and Public Research Advisory Group will meet at least 10 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 trial is designed to ensure that every person eligible to take part is offered the same opportunity regardless of demographics, social and economic factors and health status. However, there are risks that underserved individuals will encounter barriers to further participation at the time that they are approached for consent to continue in the trial, leading to the under-representation of disadvantaged populations during trial follow-up. We will use guidance from NIHR INCLUDE to identify under-served groups and address potential barriers to inclusion, drawing on the advice and experience of our patient and public contributors to support this process. Inclusivity will be a standing item on the agenda at all Patient and Public and Trial Management Group (TMG) meetings.

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.

10. DISSEMINATION AND PUBLICATION

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.

The success of the trial depends on the collaboration of clinicians and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

A communication strategy will be developed that involves all partners. The strategy will include identifying key stakeholders, messaging, channels for communication, coverage and frequency and potential risks and sensitive issues associated with the research. 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. These outputs will describe: the clinical and cost effectiveness of TI versus SGA for adults who have had an in-hospital cardiac arrest; patient and public involvement in the research; methodological and operational insights gained; wider implications for service delivery and future international guidelines.

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