Cluster randomised trial of the clinical and cost effectiveness of the i-gel supraglottic airway device versus tracheal intubation in the initial airway management of out of hospital cardiac arrest

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Glossary / abbreviations

AHA	American Heart Association
BRI	Bristol Royal Infirmary
CAD	Computer aided dispatch
CAG	Confidentiality Advisory Group
CCU	Cardiac care unit
COMET	Core Outcome Measures in Effectiveness Trials
CPR	Cardiopulmonary resuscitation
CRF	Case report form
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data monitoring and safety committee
ECG	Graphical representation of electrical activity of the heart over time, as recorded by an electrocardiograph
ERC	European Resuscitation Council
EQ5D	A standardised instrument for use as a measure of health outcome
GWAS	Great Western Ambulance service
HES	Hospital Episode Statistics
HSFC	Heart and Stroke Foundation of Canada
IAHF	Inter American Heart Foundation
ICH-GCP	International conference for harmonisation of good clinical practice
ICU	Intensive care unit
JRCALC	Joint Royal Colleges Ambulance Liaison Committee
ILHCO	International Liaison Committee on Resuscitation
MeSH	Medical Subject Headings
MRC	Medical Research Council
mRS	modified Rankin Scale
NHS	National Health Service
NICE	National institute for Health and Care Excellence
NIHR	National Institute for Health Research
OHCA	Out of hospital cardiac arrest
PIL	Participant information leaflet
QALYs	Quality adjusted life years
RCA	Resuscitation Council of Asia
RCSA	Resuscitation Council of Southern Africa
RCT	Randomised controlled trial
REC	Research ethics committee
ROLE	Recognition of Life Extinct

ROSC	Return of spontaneous circulation
SAD	Supraglottic airway device
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SMG	Study management group
SOP	Standard operating procedure
TSC	Trial steering committee
UK	United Kingdom

1. Trial summary

Cardiac arrest occurs when the heart beat and breathing stop suddenly, and is one of the most extreme medical emergencies. Health outcomes are poor; 90% of patients die at the scene or before discharge from hospital. The best initial treatment is cardiopulmonary resuscitation (CPR); a combination of rescue breathing and chest compressions. Prompt and effective CPR prevents damage to the brain and other organs, and maximises the chance that the heart will start beating again.

Ensuring a clear airway, whilst interrupting chest compressions as little as possible, is essential for survival. At the moment, we do not know the best way for NHS ambulance staff to provide rescue breathing during a cardiac arrest (out of hospital cardiac arrest: OHCA). Placing a breathing tube in the windpipe (intubation) has been considered the best method. However, attempting to place the breathing tube can cause significant complications as well as interruptions in chest compressions (thus reducing delivery of blood and oxygen to the brain and heart).

National recommendations suggest using a newer method: insertion of a supraglottic airway device (SAD); a tube that sits on top of the voice box. SADs are already used during routine anaesthesia in hospital; in emergency care, they are quicker to insert and cause less interruption to chest compressions. However, a SAD does not stay in place as securely as a breathing tube and, if a patient vomits, a SAD may not prevent stomach contents from entering their lungs.

There is real uncertainty amongst paramedics and experts in the field about the best method to ensure a clear airway during the early stages of OHCA. We therefore propose to undertake a large research study to determine whether intubation or the best available SAD (called the i-gel) gives the best chance of recovery following OHCA. The study will be a randomised controlled trial (RCT) in four English NHS ambulance services. It will recruit adult OHCA patients who have had a cardiac arrest that is not due to injury. Paramedics who agree to take part will be divided into two groups and given structured education on CPR and rescue breathing. One group will be required to use the i-gel, and the other intubation, as the first method of rescue breathing in all cases of OHCA that they attend during the study.

We will follow-up the patients in hospital, and 3 and 6 months later, to find out the quality of life of survivors and the NHS resources used during their hospital stay and subsequently. We have recently completed a highly successful preliminary study which has shown that this research is possible. We enrolled more than 600 OHCA patients, and showed that paramedics could deliver the trial as planned, obtaining all the necessary information. We also tested two different SADs, and identified the best-performing device (the i-gel) for use in this study.

The research team comprises experienced clinicians in pre-hospital, emergency and critical care, as well as expertise in the development and dissemination of international resuscitation guidelines. This clinical expertise is complimented by the research expertise of an established Clinical Trials Unit, the UKCRC registered Clinical Trials and Evaluation Unit (CTEU) and a Health Economics Research Centre, including experts in study methods, statistics, health economics and outcome assessment. The research group has strong patient and public involvement, and good links with ambulance services and experts in the field within the UK and internationally. The results from this study (AIRWAYS-2) will shape future OHCA guidelines and will yield real benefits to future OHCA patients in the UK and throughout the world.

2. Background

The UK has the highest reported incidence of OHCA in Europe, at 123 cases per 100,000 population per annum [1]. Despite recent improvements, survival rates remain poor with estimates of between 5% and 25% surviving to hospital discharge internationally, and approximately 7%-9% in the UK [2-5]. Around 6% of all intensive care bed days are occupied by patients who have suffered a cardiac arrest[6], and the average intensive care length of stay for this patient group is steadily increasing with a current mean in excess of 5 days .

During a cardiac arrest, the brain is exposed to a variable period of hypoxaemia and ischaemia, which may result in death or survival with cognitive deficits [7]. Six months after OHCA, cognitive deficits can still be detected in up to half of all survivors [8]. Hypoxic-ischaemic brain injury also has an impact on other important aspects of life. Survivors report symptoms of depression, dependency on others for daily functioning and a lower quality of life [9, 10]. Optimal CPR is one of the key factors associated with avoiding or minimising neurological impairment in the survivors of OHCA, and early effective airway management is fundamental to this. Effective ventilation maintains blood oxygenation, thereby reducing hypoxaemia and reducing the risk of brain damage [11, 12], and is associated with both return of spontaneous circulation (ROSC) and neurological recovery following cardiac arrest[11]. This increases the number of survivors and the quality of survival, with decreased dependency on acute and long-term care. Importantly, however, efforts to secure effective ventilation should not prejudice the continuous chest compressions that support the circulation and that are also essential for long-term survival.

Effective CPR with airway management improves survival and health related quality of life [13, 14]. The first few minutes of CPR are critical; early ROSC is associated with better long-term neurological outcome[15, 16]. Traditional teaching suggests that tracheal intubation (intubation) is the best way to manage the airway during OHCA [17]. However, this assumption has never been well tested [14], and pre-hospital intubation attempts by paramedics are associated with important complications: interruptions in chest compressions, unrecognised oesophageal intubation, compromised oxygenation and delays in accessing definitive care [18, 19].

Supraglottic airway devices (SADs) are an alternative to intubation. They are faster and easier to place and may reduce the complications described above [20]. SADs are used safely, effectively and frequently in hospital procedures [21-23]. They are now widespread in NHS ambulance services; in 2011/12 the London Ambulance Service reported 1,439 successful OHCA intubations, compared to 1,570 successful SAD placements[5]. Equipoise between the two techniques has led to recent calls for a large RCT of the two approaches [24, 25], which we propose to undertake.

2.1 Existing Evidence

Clinical trials registers and the databases CINAHL, Cochrane, EMBASE, Medline were searched using relevant Medical Subject Heading (MeSH) terms. The only relevant research identified was our own feasibility study, which was undertaken to prepare for and inform this study. In this feasibility study we completed 12 months of data collection in a single NHS ambulance service, and recruitment of both paramedics (184) and patients (615) exceeded our pre-determined targets.

Complete data sets were collected for >95% of patients enrolled in the trial, with overall protocol adherence in excess of 90%. As expected, the relatively small sample size meant that there were no statistically significant differences between study groups in the proportion of patients transported to hospital, with ROSC, surviving to hospital discharge or surviving to 90 days. However, we have demonstrated that our proposed trial design is feasible, and have gained important insights that have informed the design of this trial. We also have a data set on over 600 OHCA patients with comprehensive follow-up and cost effectiveness data.

Work to define a core outcome data set for OHCA, using Core Outcome Measures in Effectiveness Trials (COMET) methodology (see http://www.comet-initiative.org/), is ongoing but is not expected to report for several years; in the meantime, survival, residual disability, quality of life, process measures and cost effectiveness are the most important outcomes on which to focus.

2.2 Relevance to the NHS / health policy

Evidence-based interventions to improve OHCA survival are required urgently, but survival alone is insufficient to describe the full benefits of any improvements in care. Functional status and quality of life following OHCA are recognised as key outcome measures for resuscitation success [66,67].Therefore research to improve survival, and the quality of that survival, remains highly relevant and important to the needs of the NHS, to patients, and to the public.

This study has the potential to improve the quality of CPR, survival rates from OHCA and the quality of that survival; with reduced length of stay, enhanced quality of life and reduced use of health and social care resources. We anticipate potential gains for individual patients, the wider NHS and society as a whole.

This study is likely to lead to rapid and important changes in the treatment protocols recommended by the International Liaison Committee on Resuscitation (ILCOR). This organisation was formed in 1992 to provide an opportunity for the major groups engaged in resuscitation worldwide to work together on CPR and emergency cardiovascular care protocols. ILCOR is composed of the American Heart Association (AHA), the European Resuscitation Council (ERC), the Heart and Stroke Foundation of Canada (HSFC), the Australian and New Zealand Committee on Resuscitation, the Resuscitation Council of Southern Africa (RCSA), the Resuscitation Council of Asia (RCA) and the Inter American Heart Foundation (IAHF). As a result it has truly international reach, and its guidelines are almost universally accepted as being the most up to date and effective in the field.

3. Aims and objectives

Aim:

To determine whether the i-gel, a second-generation SAD, is superior to tracheal intubation in non-traumatic OHCA in adults, in terms of both clinical and cost effectiveness.

Objectives:

1. To estimate the difference in the primary outcome of modified Rankin Scale (mRS) at hospital discharge (or 30 days post OHCA) between groups of patients managed by paramedics randomised to use either the i-gel or intubation as their initial airway management strategy following OHCA.

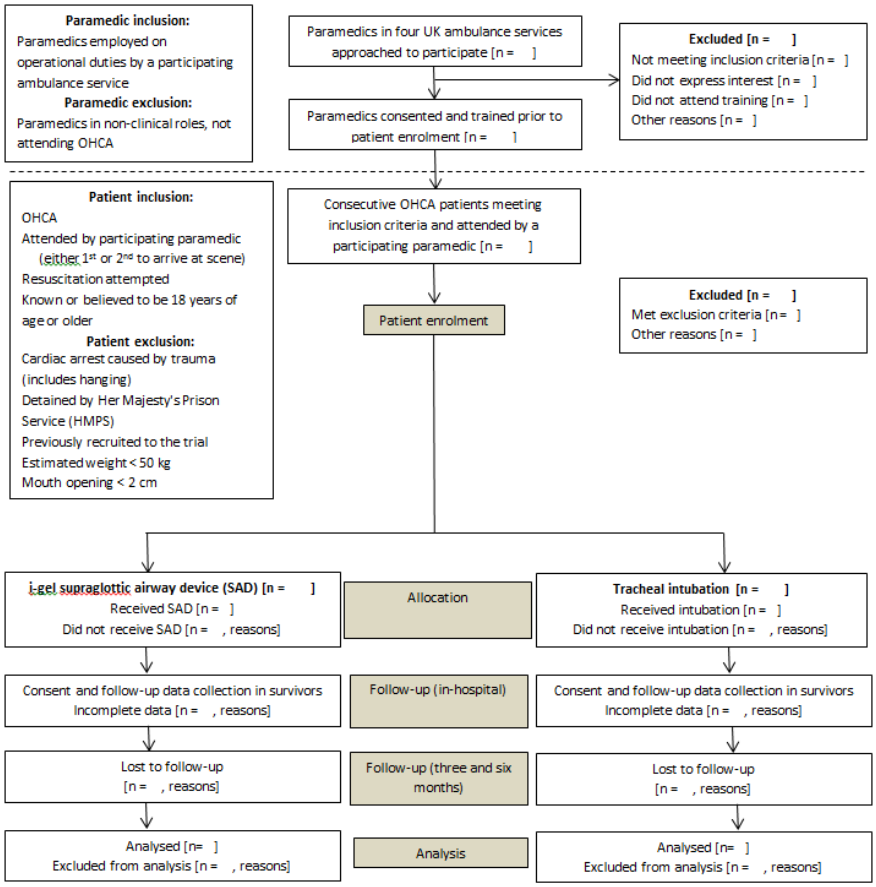
2. To estimate differences in secondary outcome measures relating to airway management, hospital stay and recovery at 3 and 6 months (see section 4.6.2) between groups of patients managed by paramedics randomised to use either the i-gel or intubation.

3. To estimate the comparative cost effectiveness of the i-gel and intubation, including estimating major in hospital resources and subsequent costs (length of stay, days of intensive and high dependency care, etc.) in each group.

4. Plan of Investigation

4.1 Trial schema

Figure 1: Trial schema



4.2 Trial design

This is a parallel two-group multi-centre cluster randomised controlled trial (RCT) and accompanying cost-effectiveness analysis to identify the best approach to initial airway management during OHCA. Randomisation by patient is impractical; we will therefore randomise by paramedic.

Paramedics will be recruited from four NHS ambulance services with favourable characteristics.

The NHS ambulance services are:

- South Western Ambulance Service NHS Foundation Trust (SWAST)
- East of England Ambulance Service NHS Trust
- East Midlands Ambulance Service NHS Trust

- Yorkshire Ambulance Service NHS Trust

The College of Paramedics is also fully supportive of the study.
Hospitals receiving OHCA patients from these ambulance services will also be taking part.

4.3 Key design features to minimise bias

4.3.1 Selection bias/allocation bias (systematic differences between baseline characteristics of the groups that are compared)

This type of bias is usually ruled out by concealed randomisation in a trial that randomises individual patients. This is not necessarily the situation with a cluster-randomised trial because inclusion of only a small number of clusters can cause chance imbalances (not bias *per se*) between the groups. Since AIRWAYS-2 will recruit about 1300 paramedics chance imbalances will not be a problem.

Even with concealed allocation of clusters (paramedics), bias can arise from recruitment of a different proportion of eligible individuals among paramedics allocated to different airway management strategies. Moreover, even if these proportions do not differ overall, differential recruitment of eligible individuals among paramedics may happen, with paramedics assigned to different airway management strategies recruiting different kinds of patients (but the same overall proportion). In this trial, we will avoid this bias by using a combination of methods to identify all eligible patients, including direct notifications by ambulance clinicians and review of routine ambulance service data to ensure >99% of the eligible patients are included (see section 5.6.1)

Bias could also be introduced by applying inclusion criteria in a biased manner, i.e. including >99% of eligible patients will not be sufficient if paramedics in different groups consider different patients to be eligible. The most obvious source of such bias is the application of a differential threshold for resuscitation by paramedics assigned to different airway management strategies, since they will not be blinded. We will use several strategies to prevent this bias from occurring, to detect it if it happens, and to correct it if necessary (see sections 4.4.2 and 5.3.7 for details).

4.3.2 Performance bias (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest).

This bias will be minimised by:

- defining the intervention and comparator, as well as standard protocols for other procedures undertaken during the trial (see sections 4.5 and 5.11);
- blinding staff beyond ED (section 5.2.2) to method of initial airway management (see section 5.2.2) and assessing the success of blinding (see section 5.2.2);
- monitoring adherence to the protocol (see section 7.1 and 7.2).

4.3.3 Detection bias (systematic differences between groups in how outcomes are determined)

This bias will be minimised by:

- using an objective primary outcome measure (modified Rankin Scale, see section 5.6);

- blinding individuals assessing outcomes (see section 5.2.2).

4.3.4 Attrition bias (systematic differences in the availability of outcome data between groups)

This bias will be minimised by:

- obtaining almost complete follow-up. About 90% of patients will not survive to hospital discharge. We expect to be able to account for all other patients who consent to follow-up from the time of discharge up to six months

4.3.5 Reporting bias

- This type of bias will be minimised by having pre-specified outcomes (see section 4.6) and a pre-specified analysis plan (see section 6).

4.4 Trial population

Adults who have suffered an OHCA that is not due to trauma. This group comprises the large majority of OHCA patients.

4.4.1 Inclusion and exclusion criteria for paramedics

Paramedic Inclusion Criteria

- Employed or soon to be employed by one of the four participating ambulance trusts in general operational duties, and could therefore be despatched to attend an OHCA as the first or second paramedic to arrive at the patient's side.
- Qualified to practice tracheal intubation in their current clinical role

Paramedic Exclusion criteria

- Paramedics working in non-clinical and managerial roles not routinely* attending OHCA

*Routinely is defined as usually attending at least 2 OHCA patients where resuscitation is attempted each year. This however will not be a 'hard' exclusion criterion.

4.4.2 Inclusion and exclusion criteria for patients:

Patient Inclusion Criteria

- Patient known or believed to be 18 years of age or older
- Patient has had a non-traumatic cardiac arrest outside hospital
- Patient must be attended by a paramedic who is participating in the trial and is either the 1st or 2nd paramedic to arrive at the patient's side.*1
- Resuscitation is commenced or continued by ambulance staff or responder*2

*1. The participating paramedic will manage the patient's airway, according to their allocation. If both the 1st and 2nd paramedic are participating in the trial, the patient's airway will be managed according to the allocation of the 1st paramedic to arrive at the patient's side (usually designated as the "attendant" within the ambulance service).

If the 1st paramedic to arrive is not an AIRWAYS-2 paramedic, but the 2nd paramedic is, the patient will be enrolled in the study unless an advanced airway intervention has already occurred (advanced airway intervention is defined as either a SAD or tracheal tube being present in the patient's mouth) at the point that the second paramedic arrives at the patient's side.

If a 3rd or subsequent paramedic arrives at the patient's side, and the first two paramedics are not participating in the trial but the 3rd or subsequent paramedic is participating, the patient will be excluded (such an exclusion may need to be determined retrospectively).

*2 Circumstances in which resuscitation should and should not be attempted are described in national guidelines. The Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Recognition of Life Extinct (ROLE) criteria are currently used by all ambulance trusts to determine when a resuscitation attempt is inappropriate, and these criteria will be applied in this trial. These criteria are objectively defined, but the frequency of attempted resuscitation in both groups will be regularly examined by the DMSC to identify any bias in the commencement of resuscitation attempts.

Patient Exclusion criteria

- Patient detained by Her Majesty's Prison Service
- Previously recruited to the trial (determined retrospectively)
- Resuscitation considered inappropriate (see below)
- Advanced airway management inserted by another HCPC registered paramedic, doctor or nurse already in place when AIRWAYS-2 paramedic arrives at patient's side (when the first paramedic to arrive is not participating in AIRWAYS-2)
- Known to already be enrolled in another pre-hospital randomised trial
- Mouth opening <2 cm

This last exclusion has been applied because SADs are not designed for use in patients with significantly reduced mouth opening. There is a risk of post-randomisation bias being introduced by this exclusion criteria, but in our feasibility study only 2/711 patients (0.3%) were excluded on these grounds. We will monitor this exclusion, under the guidance of the DMSC, and should the exclusion rate exceed 1% we will take action to address this through enhanced training and supervision.

Standardised guidelines, based on those produced by JRCALC, will be applied to determine patients for whom a resuscitation attempt is inappropriate. This is the case when there is no chance of survival, the resuscitation attempt would be futile and distressing for relatives, friends and healthcare personnel and where time and resources would be wasted undertaking such measures. When any one or more of the following conditions exist, resuscitation and enrolment in the trial will not take place.

1. massive cranial and cerebral destruction
2. hemicorporectomy
3. massive truncal injury incompatible with life (including decapitation)

4. decomposition/putrefaction
5. incineration
6. hypostasis
7. rigor mortis
8. A valid do not attempt resuscitation order or an Advanced Directive (Living Will) that states the wish of the patient not to undergo attempted resuscitation
9. When the patient's death is expected due to terminal illness
10. Efforts would be futile, as defined by the combination of **all three** of the following being present
    (a) More than 15 minutes since the onset of collapse
    (b) no bystander CPR prior to arrival of the ambulance
    (c) asystole (flat line) for >30 seconds on the ECG monitor screen. Exceptions are drowning, drug overdose/poisoning
11. Submersion of adults for longer than 1 hour

Patients will also be excluded from the study if an immediate family member, relative or close friend that is present at the scene of the cardiac arrest indicates to the participating paramedic at the start of the resuscitation attempt that the person has previously expressed an opinion that they would not wish to take part in the AIRWAYS-2 trial.

4.5 Trial interventions

4.5.1 Control group

The current standard care pathway is tracheal intubation: the placement of a cuffed tube in the patient's trachea (windpipe) to provide oxygen to the lungs and remove carbon dioxide. Tracheal intubation is considered the "gold standard" of airway management, and is used universally in comatose survivors of cardiac arrest following their admission to hospital.

4.5.2 Intervention group

The intervention being studied is the insertion of an i-gel, a second-generation SAD, as an alternative to tracheal intubation.

First introduced in the 1980s, SADs have been improved recently to reduce the risk of vomit entering the lungs and to enhance the airway seal. SADs have proved safe and effective during hospital procedures, and are now used more often than tracheal intubation in United Kingdom operating theatres [15]. Over the past decade use of SADs has also become widespread in NHS ambulance trusts. There is however substantial equipoise between the two techniques. This fact enables the proposed trial to proceed ethically, and also supports its practical delivery in UK ambulance Trusts.

Because of its speed and ease of insertion, and the fact that it does not require a cuff to be inflated, the i-gel has emerged as the preferred SAD for use during OHCA in Europe [26, 27]. We will use the most recent version of this device: the 'i-gel Pack'.

4.5.3 Aspects of management common to both groups:

For both the control and intervention groups a standardised algorithm will be used to guide further actions should the initial approach to airway management prove unsuccessful. Algorithms already exist in the different ambulance trusts, but these will need to be adapted to provide a standardised one which can be used consistently across the 4 ambulance regions. Participating paramedics will be trained in this algorithm before recruitment commences, with a refresher at the mid-point of patient enrolment. The use of such an algorithm reflects routine practice, in that paramedics will usually follow a specified protocol or "airway ladder" when managing the airway during OHCA. This approach will standardise care in each trial arm, and all other elements of the care pathway will be identical.

Care will proceed as normal for OHCA patients enrolled in the trial, aside from the initial airway management. All other interventions will proceed according to standard resuscitation guidelines that are disseminated widely in the United Kingdom and internationally.

Patients who die at the scene will be managed in accordance with nationally disseminated ambulance service protocols (e.g. recognition of life extinct, or confirmation of death). The remaining survivors will be transported to hospital, with approximately half of these admitted to an intensive care unit (ICU). These patients will be treated using standard post-OHCA care pathways.

4.6 Primary and secondary outcomes

4.6.1 Primary outcome

The primary outcome will be the modified Rankin scale (mRS) score measured at hospital discharge. However if the patient remains in hospital for more than30 days after the OHCA, the primary outcome (mRS) will be assessed at the 30 day time point instead of at discharge. The mRS which incorporates survival to discharge is widely used in OHCA research[28, 29]. mRS is usually presented dichotomously as good recovery (0-3) or poor recovery/death (4-6).

All enrolled patients are eligible. We will collect survival data and mRS at hospital discharge with the prior permission of the Health Research Authority Confidentiality Advisory Group (CAG), thereby ensuring close to 100% data ascertainment.

For patients that survive to hospital discharge (or are still inpatients 30 days after their OHCA) the mRS will be determined by a research nurse who will assess the patient using a simple flow chart that has been previously used to assess patients who have had a cardiac arrest[30]. Any patient who does not survive to discharge will automatically be assigned a score of six (dead) .

4.6.2 Secondary outcomes

We will seek consent from survivors (or a consultee according to the requirements of the Mental Capacity Act 2005 if the patient lacks capacity) to collect additional data at hospital discharge and 3 and 6 months after OHCA (depending which consent option the participant choses-see section 9.7.1). We have chosen a 6-month final follow-up because, whilst there are very few additional deaths between 3 and 6 months, quality of life and functional independence in activities of daily living continue to improve during this time [31].

All enrolled patients

1. Initial ventilation success, defined as visible chest rise.
2. Regurgitation/aspiration.
3. Loss of a previously established airway.
4. Actual sequence of airway interventions delivered.
5. Chest compression fraction (one ambulance region only, see below).
6. Return of spontaneous circulation (ROSC).
7. Airway management in place when ROSC was achieved or the resuscitation was discontinued.
8. Economic data regarding expenditure and further healthcare contacts.

Patients who survive to admission to hospital (estimated 20% of enrolled patients)

9. Length of intensive care stay.
10. Length of hospital stay.

Patients who survive to hospital discharge (estimated 9% of enrolled patients)

11. Quality of life (using the EQ-5D) at hospital discharge

Patients who survive beyond hospital discharge

12. Date of death (if applicable)
13. Modified Rankin scale at 3 and 6 months following OHCA
14. Quality of life (using the EQ-5D) at 3 and 6 months following OHCA.

Good quality, continuous CPR is associated with increased survival and improved neurological outcomes following cardiac arrest [24, 32], and the concept of compression fraction has been developed as a standardised way of measuring and expressing this [33]. The compression fraction is defined as the proportion (or percentage) of resuscitation time without spontaneous circulation during which chest compressions are administered: the higher the compression fraction the better the quality of CPR, and the more likely the patient is to survive [34]. Comparing the compression fraction between the two randomisation arms may help to explain the study findings. Measuring and reporting compression fraction allows heterogeneity between trials to be more consistently described. A suggested mechanism by which SADs may improve outcome from OHCA is a reduction in interruptions to CPR (with an accompanying increase in compression fraction)

Compression fraction is not routinely measured during OHCA in England, but is technically possible [35]. Measurement of compression fraction requires the use of modified defibrillator-monitors, we do not believe it is practical, or affordable, to measure this in all enrolled patients. Instead, we will implement technology that allows compression fraction to be routinely measured during CPR in a sub-set of enrolled patients (for example in one of the four participating ambulance trusts) and collect these data alongside the other outcome measures. This will enable compression fraction to be compared in a subset of the two trial arms, and will also benefit future studies by introducing and evaluating the technology required to routinely measure compression fraction during OHCA.

4.7 Sample size calculation

In our feasibility study 9% of recruited patients survived to hospital discharge, and this is the current rate of overall survival to discharge reported by English ambulance trusts (see:

http://www.england.nhs.uk/statistics/statistical-work-areas/ambulance-quality-indicators/ambqi-2012-13/). A 2% improvement in the proportion of patients achieving a good neurological outcome (mRS score of 0-3) would be clinically significant, and similar to the 2.4% difference in survival to discharge between tracheal intubation and SADs reported in a recently published retrospective analysis [18].

To identify a difference of 2% (8% vs. 10%, i.e. centred on 9%) requires 4,400 patients per group (at the 5% level for statistical significance and 90% power). However, each OHCA is not an independent observation, as the patients are nested within a limited number of attending paramedics. Using data from our feasibility study of 171 paramedics attending 597 OHCA, we estimated the intraclass correlation (ICC) to be <0.001. However, when estimating the sample size we have assumed a conservative estimate for the ICC of 0.005. We estimate that 1,300 paramedics will participate; this gives an adjusted sample size of 4,535 patients per group (9,070 in total). In our feasibility study the mean number of patients enrolled per participating paramedic was 3.6 per year, which translates to 7 patients per paramedic over our planned two-year recruitment period (7 x 1,300 = 9,100).

In the feasibility study within the Great Western Ambulance Service 171 from 535 eligible paramedics (32%) agreed to take part. The total pool of eligible paramedics across the four ambulance trusts participating in Airways-2 is more than 4,300, and 32% of this total provides more than 1,350 participating paramedics.

5. Trial methods

5.1 Description of randomisation

OHCA is an extreme medical emergency requiring immediate attendance and action by skilled paramedic staff in a wide range of unpredictable environments. For this reason, the procedures that would be required to achieve randomisation by patient (contacting a remote server or telephone line, or even opening a sealed opaque envelope) are impracticable at the point when an eligible patient is identified. Indeed, almost all similar research studies have been cluster-randomised, often at the level of ambulance stations [36-38]. This in turn has led to concerns regarding compliance and bias, and for this reason our team has investigated the principle of randomisation by paramedic.

Randomisation of paramedics has the advantage of producing a large number of relatively small clusters (each paramedic is a cluster), which more closely approaches individual patient randomisation, and also supports effective stratification so that the characteristics of randomisation groups are more likely to be similar. In our feasibility study we used this approach successfully. Randomisation will be stratified by ambulance trust, clinical experience and the location of the paramedic's base ambulance station. This will ensure balance of clinical expertise of the attending paramedic, and ambulance response times relating to an urban or rural environment, across the two groups, thereby increasing the likelihood that baseline characteristics of patients will be balanced.

Paramedics who consent to take part in the study will be randomised to the i-gel or the intubation after they have consented but before they start trial group specific training. Randomisation will be performed using an in-house computer based system with secure allocation concealment that cannot be changed once allocated, and will allocate the paramedics in a 1:1 ratio to the two groups.

Randomisation will be carried out by a member of the CTEU Bristol, or appropriately trained member of the research team.

Code breaking will not be necessary since paramedics will be aware of their allocation, and whilst the intervention is in progress the allocated treatment will be apparent. Furthermore, once the intervention has been completed subsequent in-hospital treatment is not influenced by study allocation.

5.2 Procedures to minimise bias

5.2.1 Selection/allocation bias

First, established objectively defined criteria will be used by participating paramedics to determine whether a resuscitation attempt is appropriate, and hence whether the patient is eligible (see standardised resuscitation guidelines, section 4.4.2).

Second, we will institute a programme of regular monitoring by analysing the proportion of cardiac arrests recruited, to detect any imbalances that may be caused by different thresholds for resuscitation. We will also monitor the presenting rhythm, proportion of witnessed and un-witnessed arrests, presence of bystander CPR and time from 999 call to crew arrival.

If we suspect that a different threshold for resuscitation is being applied by one or more paramedics participating in the trial, the first step will be to identify the personnel involved and ensure that their training in the trial procedures is up to date, and reinforce the essential messages about the rationale for the trial. The trial team will include a local research paramedic in each of the 4 ambulance regions, this person will develop a close working relationships with the participating paramedics, and will be ideally placed to undertake this role.

5.2.2 Blinding

Because of the nature of the intervention, ambulance clinicians cannot be blinded, and will be aware of treatment allocations, with an attendant risk of performance bias. However control room personnel will be blinded to the allocation of paramedics, and follow established protocols when allocating resources to a possible cardiac arrest. This will ensure that there is no bias in despatch.

Patients will be unaware of their treatment allocation at the time of the intervention, and this is likely to be maintained throughout the trial. Research staff assessing outcomes at hospital discharge and at the 3 and 6 month follow-up will also be blinded to treatment group and this will be formally assessed during the study. Blinding of participants and clinical personnel will minimise performance bias.

Unfortunately emergency department staff cannot be blinded to which treatment arm (intubation or i-gel) the patient was allocated to, as the patient will arrive in the ED with either intubation tube or i-Gel in situ, with the difference between them being visually apparent. We will however be able to blind clinical staff, whom care for the patient beyond ED to the method of initial airway management used. Therefore the care of the patient beyond the emergency department will not be affected by knowledge of the intervention used.

5.3 Research procedures

5.3.1 Training of Paramedics

Standardised training materials (including learning objectives and lesson plans) have been developed to support training in research procedures and the allocated airway management technique for both the control and intervention groups. These will be administered to all participating paramedics before enrolment commences, with a research refresher halfway through the recruitment period (at 12 months). Concerns have been raised that after two years using one method of airway management participating paramedics risk becoming de-skilled in alternative approaches, and therefore to support effective paramedic recruitment and retention we will offer additional "exit" training to all participating paramedics to update their airway skills once patient enrolment has been completed.

Alongside this training we will institute a range of measures to encourage and promote ongoing participation and momentum amongst paramedics. These will be adapted from previously successful research in ambulance trusts and will include a study newsletter, regular publicity and updates, marking of key milestones and formal recognition of success. We have also secured a formal endorsement from the College of Paramedics in supporting the recruitment and retention of participating paramedics, and disseminating the study results.

The first training session will consist of generic training on resuscitation and the study procedures, data collection and we will explain the trial, equipoise and the need to follow protocol. We will then invite paramedics to sign a consent form or leave training, without prejudice. We will randomise paramedics who have consented to take part in the trial to one of the two groups (i-gel or intubation). The paramedics will then be divided into two groups according to their allocation, and complete technical training specific to each trial group. We will then answer any questions that have arisen and complete the training session.

5.3.2 Tracheal Intubation

Tracheal intubation requires the use of a laryngoscope to see the patient's larynx, followed by the placement of a tube at the correct level in the trachea, and is usually undertaken only by doctors and paramedics. The ease with which tracheal intubation can be accomplished varies from patient to patient, and it requires training to develop this skill, followed by ongoing practice to ensure that the skill is maintained. Sometimes tracheal intubation cannot be achieved, or the tracheal tube may be placed in the patient's oesophagus by mistake. If the latter circumstance goes unrecognised the patient is unlikely to receive any oxygen during their cardiac arrest and it is well recognised that, even if a tracheal tube is correctly placed, the technical demands of achieving intubation can lead to long pauses in the chest compressions that are vital to resuscitation success [18]. To ensure that the standard care pathway is optimised, and the chance of successful tracheal intubation maximised, all participating paramedics will be equipped with an intubating bougie and end-tidal carbon dioxide monitoring.

5.3.3 Placement of i-gel

Placement of an i-gel is much simpler than tracheal intubation, and does not require the use of a laryngoscope. The i-gel device is simply inserted, in the correct orientation, into the patient's mouth and pharynx, where it usually provides a direct channel from the mouth to the opening of the trachea. Sometimes however the i-gel will not form a satisfactory seal, leading to leakage and a failure to

ventilate the lungs. There is also a risk that gastric contents (vomit) will regurgitate and enter the lungs (this is prevented by the cuff on a tracheal tube), or that the i-gel will dislodge if the patient is rolled or moved and so the training of the paramedics in the correct placement of the I-gel is very important.

5.3.4 Use of study devices

The study devices are only to be used by paramedics for patients fulfilling the eligibility criteria for the trial. The devices are supplied and approved for the trial only, and paramedics have access to standard airway equipment to use in other situations.

5.3.5 Measurements of compression fraction:

Previously compression fraction has been measured by fitting general packet radio service modems to compatible Lifepak 15TM defibrillators used by paramedics, and automatically transmitting a download of CPR data after each OHCA (to which paramedics are blinded) for subsequent remote analysis by a research team using freely available software [35]. We intend to use a similar approach in this study, tailored to the defibrillators and supporting technology available.

5.4 Duration of treatment period

The duration of treatment will be the pre-hospital phase of an enrolled patient's cardiac arrest; likely to be between 15 and 90 minutes.

5.5 Definition of end of trial

For individual patients the trial will end after the final follow-up, six months after the index cardiac arrest (for patients consented under option A or B) or immediately after approach for consent for patients who select option C or do not respond when approached to consent. The trial as a whole will end once all participants have completed the follow-up phase or have been lost to follow-up. This will be six months after the last patient is enrolled in the study.

5.6 Data collection

Data collection will include the following elements:

a) A log of all paramedics approached and a record of those who consent to take part in the study

b) A log of all patients that have an OHCA who are attended by a paramedic within one of the four participating ambulance trusts.

c) A log of those attended by an AIRWAYS-2 paramedic (together with details of whether resuscitation was attempted)

d) A log of all OHCA patients attended by an AIRWAYS-2 paramedic (where resuscitation is attempted) assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.

e) A screening log of all OHCA patients enrolled in the study who survive to ICU/ cardiac care unit (CCU) discharge

f) Survivors who are approached for consent (including the date when they are given the patient participant information leaflet (PIL)) and outcome of the consent process.

g) For those who consent to active follow-up, responses to quality of life and mRS questionnaires collected at time of consent and at follow-up at 3 and 6 months.

h) Key data items from routine data sources for survivors who consent and for those who die prior to discharge from ICU/CCU.

i) Demographic characteristics of surviving OHCA patients who do not consent and withdraw from the study. These data will be requested without any patient identifiers in order to maintain anonymity. The following information will be sought:
   -NHS number
   -date of birth
   -sex
   -data to characterise socio-economic status (partial postcode)

Data collection will occur during the out of hospital treatment phase, during the inpatient phase of care, at hospital discharge and at 3 and 6 months (± 4 weeks) after the index OHCA (Table 1).

Training in data collection and case report form (CRF) completion will be provided by the research nurse in each region, coordinated and supported by the central study team. A fixed fee per patient has been included in the study research costs to support the collection of study-specific outcome data.

Table 1 Summary of data items and data collection points

Data item	Out of hospital treatment phase *(data collection by paramedics)*	Hospital discharge *(data collection by hospital staff)*	3 month post OHCA	6 month post OHCA
Eligibility	✓			
Airway management	✓			
Demography	✓	✓		
Survival	✓	✓	✓	✓
Patient movements	✓	✓		
Approached for consent		✓		
Modified Rankin Scale		✓	✓	✓
EQ-5D		✓	✓	✓
Economic data	✓	✓	✓	✓
Serious Adverse events	✓	✓	✓	✓
Length of hospital stay/ ward movements		✓		

To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria. All personnel carrying out outcome assessment beyond the emergency care department care will be blinded; this will minimise detection bias.

5.6.1 Identification of patients with OHCA

For this study we are using a model of deferred consent for survivors. All eligible patients attended by a participating paramedic will be automatically enrolled in the study. Therefore, to avoid bias, it is essential to establish mechanisms that will reliably identify every one of these patients. We will achieve this by identifying every OHCA (where resuscitation is attempted) that occurs in the participating ambulance services throughout the study period, along with the subset of patients eligible for study inclusion. Our process to achieve this is described below. It allows regular review by the DMSC to identify any allocation bias, and also supports a complete intention to treat analysis.

In April 2011 the Department of Health for England introduced survival from cardiac arrest as part of the Ambulance Service National Quality Indicator set. Return of spontaneous circulation and survival to hospital discharge rates are reported for all patients who have resuscitation started or continued by an NHS ambulance service after an OHCA [39]. For this reason all cardiac arrests are routinely identified by English ambulance services, with regular data collection and return. This process is currently being strengthened through the introduction of an electronic patient record and a national OHCA registry, based at the University of Warwick [40]. To ensure near-complete patient identification we will use a triangulation method developed during our feasibility study. This collects data on all OHCAs occurring within an ambulance service from three separate sources:

A. Direct paramedic report: participating paramedics are asked to complete a CRF immediately after each eligible OHCA that they attend, and notify the coordinating research paramedic by telephone, text or e-mail.

B. Daily review of the ambulance computer aided dispatch (CAD) system, by a project research paramedic, to identify all 999 calls from the previous 24 hours identified as suspected or confirmed cardiac arrest, and follow-up with the relevant ambulance staff to determine whether OHCA had occurred.

C. Regular review of the OHCA data routinely collected by that ambulance trust, and reported as part of the Ambulance Service National Quality Indicator set. This is usually based on the clinical record (paper or electronic) routinely completed by ambulance staff after each case that they attend.

Source A will be the primary data source for the study. However, by triangulating data from all three sources it is possible to reliably identify all, or nearly all, OHCAs where resuscitation is attempted during the study period. Whilst it is possible for an eligible OHCA to be overlooked by this triangulation process, it would require that an arrest not be reported to the research team by a participating paramedic, not be identified as an OHCA on the CAD and not be picked up by the ambulance trust's routine identification and reporting system. We estimate that the chance of this happening is very low, thereby ensuring an exceptionally high rate of eligible patient identification that reduces selection bias to an absolute minimum.

5.6.2 Out of hospital treatment phase (data collection by paramedics)

After treating an eligible OHCA patient, the participating paramedic responsible for airway management will complete a CRF to capture baseline and secondary outcome data. The CRF will be completed at the same time as routine ambulance service paperwork: immediately after the patient has been handed over to the receiving hospital team or resuscitation attempts have been discontinued at the scene. The CRF should then be returned as soon as possible (preferably within 24 hours) to the coordinating research paramedic by a secure method chosen by each trust e.g. post, secure fax or e-mail. Occasionally the participating paramedic will not complete the form immediately, in which case they will be contacted by the research paramedic subsequently, and encouraged and supported to do so.

Even when this does not occur, relevant data can be extracted from the routine ambulance service record within 48 hours, allowing the patient to be followed up in order to obtain consent and collect primary and secondary outcome data. Ambulance services reliably collect data regarding the individuals attending each patient and the time of staff arrival: therefore for every eligible patient the attending ambulance paramedic(s), trial allocation and a range of baseline data can be determined with near 100% accuracy.

5.6.3 Hospital discharge (data collected by hospital staff)

Once a patient has been admitted to hospital the consent and follow-up process will be coordinated by a research nurse allocated to each participating ambulance service. This has been identified as a separate, hospital-based post to ensure that consent and follow-up is blinded to treatment. The research nurse will usually be based in the main “heart attack centre” or major receiving hospital for that region, since there is increasing evidence to support the centralisation and specialisation of care for the survivors of OHCA, thereby improving outcomes [41].

Survivors of OHCA tend to be transferred to such centres. Each research nurse will receive regular lists of enrolled patients who have been brought to the receiving hospitals in that ambulance service region. The research nurse will coordinate the process of identification, consent and follow-up data collection with support from the central team. Although the research nurse will undertake this personally where necessary, in the majority of cases the consent and follow-up processes will be undertaken by existing research staff at the receiving hospitals.

5.7 Source data

Source data are defined as the data held in the originating ambulance and hospital information systems. For quality of life data and questionnaires relating to mRS completed by telephone/ post/internet at follow up, the questionnaires themselves will be the source data. The source data for health resource outcomes will mainly be extracted from Hospital Episode Data. Where this is not possible, the data will be collected on the study CRF (with the source data being the patient’s medical record).

5.8 Planned recruitment rate

Recruitment is expected to take place over a 24 month period with 9,070 patients required in total (4,535 in each of the two trial groups). Recruitment will be split across the 4 ambulance trusts (section

4.2) with the number of paramedics recruited in each region being proportionate to the total number of eligible paramedics employed within that region.

This projected rate of recruitment is based on information obtained in our feasibility study. We recruited from Great Western Ambulance Service (GWAS), which had a pool of 535 eligible paramedics. GWAS was relatively small, and has since been acquired by South Western Ambulance Service, which has a pool of >1,500 eligible paramedics. The three other ambulance services that have committed to the research have a combined pool of >3,200 paramedics. Therefore, the four centres have eight times the paramedics of the feasibility study.

Based on our feasibility work we are confident we can enrol 1,200 OHCA patients per year in each of four participating ambulance trusts, giving >9,000 patients over two years of recruitment.

5.9 Participant recruitment

5.9.1 Paramedics

Paramedics in the 4 trusts who have provided formal letters of support for the study will be invited to participate in the study through a process of informed consent (Section 9.5). The study will be well publicised in participating ambulance trusts using routine communications and bulletins, supplemented by personal invitation letters, posters and awareness-raising events.

5.9.2 Patients

For this study we are using a model of deferred consent for survivors. All eligible patients attended by a participating paramedic will be automatically enrolled in the study. For details on how these patients are identified see section 5.6.1.

5.10 Discontinuation/withdrawal of participants

If a participant wishes to withdraw from the study after providing consent, we will continue to analyse any data already collected but no further data collection will take place.

5.11 Frequency and duration of follow up

Follow-up will occur at 3 and 6 months (± 4 weeks) after OHCA. The follow up will usually be carried out by telephone or as a postal or online questionnaire co-ordinated by the Bristol CTEU. If this proves to be impractical, follow up may be carried out by the research nurse and may occur in hospital, but more commonly at an outpatient appointment (ideally coinciding with routine clinical follow-up) or in the patient's home/usual place of residence. The primary and secondary outcome measures have been selected to be versatile in this regard, and have been validated for telephone administration [41-45].

5.12 Likely rate of loss to follow-up

In the feasibility study 7% of paramedics withdrew from the study during the 12 month data collection phase and 86 % of patients discharged from hospital consented to follow up at 3 months. We would expect similar figures for this study.

5.13 Expenses

A payment of overtime and travel expenses will be made to paramedics each time they attend one of the study training sessions. The initial training session is mandatory for all paramedics who wish to take part in the study and attendance at the refresher training and exit training will be strongly encouraged.

No expenses will be payable to participants because participants will not be required to make any additional visit to hospital, to their GP or to any other health or welfare professional for the study.

6. Statistical analyses

6.1 Plan of analysis

The primary outcome of mRS at discharge or 30 days post OHCA (presented dichotomously as good recovery (0-3) or poor recovery/death (4-6)), and other binary outcomes, will be analysed using a multilevel logistic regression model, in which the data are nested within attending paramedic. Repeated mRS scores will be analysed using multilevel logistic regression for repeated measures. Survival to 6 months and other time-to-event outcomes will be analysed using survival analysis methods, again allowing for clustering of patients by paramedic. Patient responses to the individual EQ-5D questions will simply be described because these will be available only for survivors. Overall quality of life utility scores and patient survival will be analysed jointly to assess whether the use of the i-gel supraglottic airway device simultaneously improves the patient's quality of life and reduces the risk of death.

Enrolled patients who are subsequently identified as being ineligible will remain within the trial and be included in analyses with the exception of a) patients who were subsequently found to have been previously enrolled in the trial; b) patients who were inadvertently enrolled in the study due to being treated as a study participant by a paramedic who arrives later than second at the patient's side; c) patients who are subsequently identified as being children (aged < 16 years); individuals aged 16 and 17 years will be included in analyses." . Analyses will be done according to the principle of intention-to-treat, and reported according to the CONSORT guidelines [46, 47].

A detailed analysis plan will be prepared and agreed with the DMSC before the database is locked and any comparisons between groups are investigated.

Non-adherence to allocated group will be documented. The trial will be analysed on an intention-to-treat basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all participants treated by a study paramedic who meet the inclusion criteria. Follow-up for the outcomes measures during the participant's stay in hospital and at the 3 month and 6 month window should be complete for all participants that consent to taking part in the study.

6.2 Subgroup analyses

Two sub-group analyses are planned: the Utstein comparator group (estimated to make up about 20% of the total) vs. non-comparator group, and arrest witnessed by ambulance staff (estimated to make up

6% of the total) or not. We will describe the outcomes in the sub-groups and test for differences in the primary outcome between subgroups by including interaction terms in the models, although we recognise that the power to detect such differences will be low as the proportions in the subgroups will be unequal.

6.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Formal interim analysis is planned at the mid-point of recruitment (after 12 months), and will be presented to the DMSC. Safety data will be reported together with any additional analyses the committee request. In these reports the data will be presented by group but the allocation will remain masked.

6.4 Criteria for the termination of the trial

The trial may be terminated early on the instruction of the trial steering committee (TSC) when following recommendations from the DMSC or if an interim analysis of the data from this trial or the results of another study supersede the necessity for completion of this study.

The trial will also be stopped prematurely if mandated by the Research Ethics Committee (REC) or if funding for the trial ceases.

The REC will be notified in writing if the trial has been concluded or terminated early.

6.5 Economic evaluation

For the economic evaluation we will follow established guidelines as set out by the National Institute for Health and Care Excellence (NICE)[48]. The evaluation will be undertaken from an NHS and personal social services perspective. A cost-utility analysis will be conducted, since the primary outcome measure for the economic evaluation will be quality adjusted life years (QALYs) [49], estimated using the EuroQol EQ-5D-5L [50, 51]. These data will be collected for all survivors at hospital discharge and 3 and 6 months after their OHCA. The EuroQol EQ-5D-5L will be administered in person by a research nurse blinded to treatment allocation at discharge. The 3 and 6 month EQ-5D will be co-ordinated by Bristol CTEU and will be administered to the patient/consultee either by telephone, or by a postal or web-based questionnaire. If this proves impractical a research nurse can administer the questionnaire to the patient/consultee at either an outpatient clinic appointment (timed where possible to coincide with routine clinical follow-up) or by visiting the patient's home.

Given that patients will be unable to complete a baseline EQ-5D-5L questionnaire, a baseline valuation will be assigned to all patients informed by the current literature. Respondents to the EQ-5D-5L will be assigned valuations derived from published UK population tariffs for the EQ-5D-3L [52]and using the crosswalk value set available from the EuroQol website (http://www.euroqol.org), or using a UK population tariff for the EQ-5D-5L if published prior to the analysis of the trial. These valuations will then enable QALYs gained per patient to 6 months to be calculated.

Resource use data will be collected on the two alternative initial airway management methods delivered by paramedics, resources used once in hospital such as targeted temperature management, interventions in the cardiac catheter laboratory (e.g. angioplasty) and intensive care unit stay. We will

also collect any resources which may be related to the patient's OHCA following hospital discharge such as hospital readmissions, outpatient and Accident and Emergency visits and contacts with general practice. Resource use data will either be extracted from the Hospital Episode Statistics (HES) data set or be collected as part of the trial CRFs up to hospital discharge. At 3 and 6 months data will be captured using bespoke resource use questionnaires. Any hospital admissions in this follow up period will also be confirmed using the HES data set . We demonstrated the ability to successfully collect these economic data during our feasibility study.

A detailed preliminary study (currently pre-publication) led by one of this proposal's co-applicants (Brett) has been performed on a dataset from the London Ambulance Service and Imperial College Healthcare NHS Trust, the latter of which is a major de facto cardiac arrest and heart attack centre in North West London. This has allowed us to develop an understanding of the likely proportions of patients surviving to the various "way-points", and to develop the CRFs to comprehensively capture the resources used, and hence the costs incurred, to then perform this patient level cost effectiveness analysis in accordance with NICE guidelines. Unit costs will be derived from nationally published sources and Trust finances, and attached to the resource use data.
Missing data will be handled using multiple imputation methods[53]. We will report the cost and quality of life data for each trial group and the difference between the groups, accounting for the effect of the clustering. From the average costs and QALYs gained in each trial group, the incremental cost-effectiveness ratio will be derived, producing an incremental cost per QALY gained of i-gel compared to intubation [54]. Given this is a cluster randomised trial, statistical methods for combining costs and outcomes will need to take account of the correlation between costs and outcomes at both the individual level and also at the cluster level [55, 56]. The i-gel will be considered cost-effective if the incremental cost-effectiveness ratio falls below £20,000, the level below which NICE generally recommends interventions to the NHS [57]. Univariate and multivariate sensitivity analyses will show what impact varying key parameters in the analysis has on baseline cost-effectiveness results. Results will be expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that the i-gel is cost-effective for different levels of willingness to pay for health gain.

7. Trial management

The trial will be managed by the Clinical Trials and Evaluation Unit (CTEU Bristol). The CTEU Bristol is an UK Clinical Research Collaboration registered Clinical Trials Unit. The CTEU Bristol will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

7.1 Day-to-day management

The trial will be managed by a study management group (SMG), which will meet by teleconference approximately monthly. The SMG will be chaired by the chief investigator and will include all members of the named research team (see Chief Investigators & Research Team Contact Details).

A trial manager will be responsible for the day-to-day running of the trial, obtaining approvals, reporting to TSC, DMSC and REC, managing the budget, drafting reports and research papers. The trial manager will report to the chief investigator regularly. They will liaise closely with the other trial staff and will ensure that all individual research components are undertaken in a timely manner and within budget.

They will undertake monitoring procedures at a level appropriate to a risk assessment performed by the sponsor to ensure delivery of the study in accordance with the protocol and the statutory instruments.

7.2 Monitoring of sites

7.2.1 Initiation visit

Before the study commences training sessions for the study research paramedics and study research nurses will be organised by CTEU Bristol. These sessions will ensure that personnel involved in the study fully understand the protocol, CRFs and the practical procedures for the study.

7.2.2 Site monitoring

The trial coordinating centre will carry out regular monitoring and audit of compliance with GCP and data collection procedures described in section 5.6.

7.3 Trial Steering Committee and Data Monitoring and Safety Committee

The TSC will meet approximately every 6 months. It will consist of an independent chair, appropriate clinical and investigator expertise and two patient representatives.

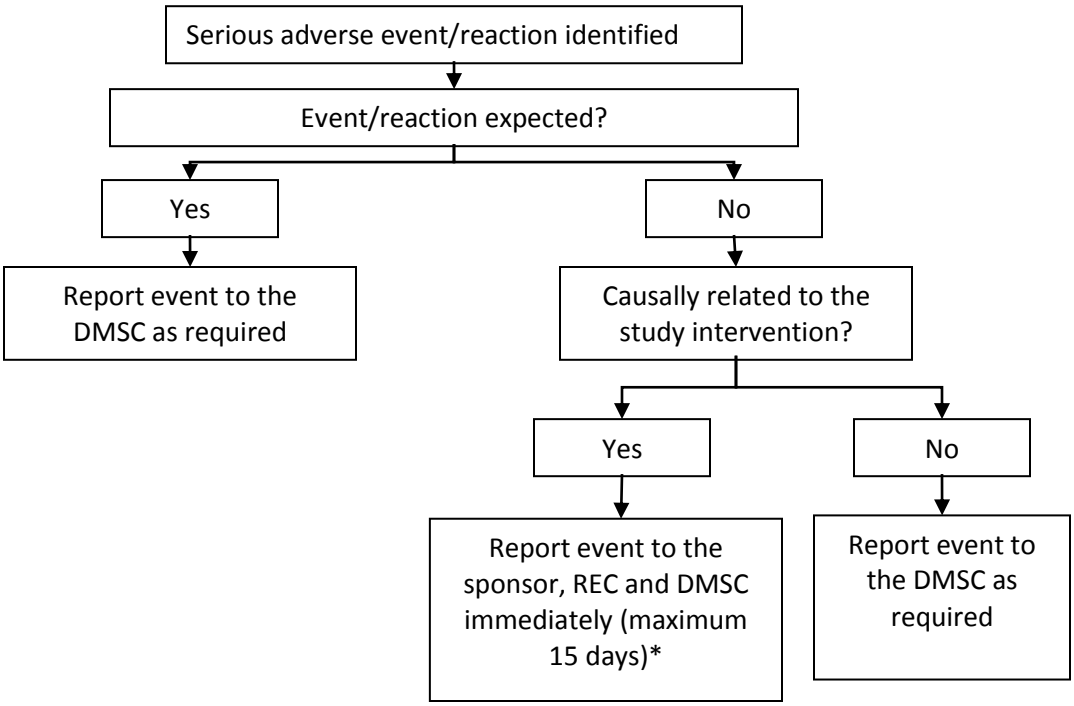
The DMSC meetings will be timetabled at points appropriate to reporting findings from the DMSC into the TSC meetings. One DMSC meeting will coincide with the formal mid-point review.
The committee will consist of an independent statistician and two independent research-active clinicians. Patient and public involvement group meetings will be held every 4 months for the study duration.

8. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy (see Figure 2).

Note: Elective surgery/interventions/treatment (e.g. planned non-cardiac surgery) during the follow-up period that was planned prior to recruitment to the trial will not be reported as an unexpected SAE.

Figure 2: Serious adverse event reporting flow chart



* These unexpected related events will also be reported to the local relevant R&D ambulance trust.

8.1 Additional terms for device trials

For trials of devices, additional terms are used, defined as follows:

- Adverse Device Effect/Event (ADE): Any unfavourable or unintended response to a medical device.
- Serious Adverse Device Effect (SADE): An ADE that has resulted in any of the consequences of a serious adverse event (SAE) or might have led to those consequences if suitable action/intervention had not been taken.
- Incident: Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which directly, or indirectly, might lead to or might have lead to the death of a patient, or user or of other persons or to the serious deterioration in their state of health.

8.2 Expected adverse events

All of the patients in this trial will be in an immediately life-threatening situation, many will not survive, and all of those that do will be hospitalised. These situations are therefore expected, and events leading to any of them should be reported as SAE/SADEs only 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 hospitalisation) should not be reported.

8.3 Unexpected adverse events

Events should be reported as SAE/SADEs only if they: are serious AND are potentially related to trial participation i.e. may have resulted from study treatment such as use of the SAD device; AND are unexpected i.e. the event is not an expected occurrence for patients who have had a cardiac arrest.

Examples of events that may be SAE/SADEs are; use of an SAD causing a new injury that endangers the patient, malfunction of the device causing injury to ambulance clinicians, malfunction of the device leading to inadequate ventilation.

8.4 Period for recording serious adverse events

Data on adverse events will be collected start of the intervention for the duration of the participant's post-operative hospital stay and for the 6 month follow-up period.

9. Ethical considerations

Research in out of hospital cardiac arrest (OHCA) is challenging because it requires the recruitment of incapacitated adults without any opportunity to achieve prior consent. The nature of the condition is such that it occurs without warning, the patient is instantaneously incapacitated and immediate treatment is an absolute priority, leaving no possibility of consultation prior to resuscitation. Furthermore, because this is a trial of initial airway management, in the first minutes of OHCA, the intervention is completed within 30-60 minutes of the cardiac arrest. Therefore, by the time consent can be sought it is not possible to decline to participate. For this reason strict ethical safeguards, robust patient and public involvement and a high degree of clinical equipoise between treatment groups is essential. This study achieves all of these, and meets the requirements of the Mental Capacity Act 2005 to proceed in the absence of prior consent. Both treatment options are currently utilised as routine care in the English ambulance trusts, and there is established uncertainty as to which is the better option.

We are fortunate to benefit from strong patient and public involvement. In our feasibility study we used a model of deferred consent for survivors, and did not inform the relatives of those patients who do not survive the initial cardiac arrest that their loved one had been enrolled in a research study. Informing relatives that their recently deceased loved one was involved in a research study has a high risk of increasing distress and uncertainty without benefit.

The ethical issues in this proposal are identical to those in our feasibility study, for which we secured approval from the Cambridge Central NHS REC: this committee has specific authority to review trials of a medical device in incapacitated individuals.

Following the acquisition of GWAS by South Western Ambulance Service we have developed a dedicated OHCA patient and public research advisory group which has already met three times and has further endorsed and developed this approach to patient consent and relative information. This group recommends that patients be approached, informed of the study and asked to consent at the time that they are discharged from the intensive care unit, or that a close relative is approached if the patient remains incapacitated at this time. This lay group has also endorsed the routine collection of anonymised core outcome data.

Recruitment of paramedics raises no particular ethical issues since they are NHS staff who are able to consider the study over a period of time and give informed, written consent.

9.1 Review by an NHS Research Ethics Committee (REC)

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK NHS REC.

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

9.2 Review by Health Research Authority Confidentiality Advisory Group (CAG)

We will seek approval from the CAG to

a) Collect data which will enable us to identify all patients who have been enrolled in the trial (see section 5.6.1). As there is no automatic linkage between ambulance service data and hospital data, variable processes have arisen ad hoc throughout England. We need to use patient identifiable data to link ambulance service data and hospital data, to verify that different records relate to the same individual and to determine survival status for each patient.

b) Collect data on treatment and outcomes to hospital discharge or death (whichever occurs first) on all OHCA patients. This approval is being sought in order to access identifiable information without consent for those patients where it is not possible to obtain consent. This approach will ensure maximum data ascertainment (see section 4.6.1).

9.3 Risks and anticipated benefits

Participating paramedics will benefit from additional training in resuscitation, airway management and evidence based practice during the trial. No potential harms to paramedics have been identified.

It is generally recognised that patients enrolled in research studies tend to have better outcomes than those not enrolled. It is possible that one study group will prove to be superior to the other, but at present clinical equipoise exists, and the trial is being undertaken to address this question. Ongoing scrutiny by the TSC and DMSC, coupled with a formal interim analysis, is designed to minimise the risk to participants, and ensure that the trial is discontinued if significant differences are identified between the two study groups.

Both interventions have recognised complications. These include:

- Interruptions to CPR. This is possibly more common with tracheal intubation.
- Misplacement of the device (particularly unrecognised misplacement). This is possibly more common with tracheal intubation.
- Regurgitation of stomach contents, and aspiration into the lungs. This is possibly more common with the i-gel SAD.

- Dislodgement of the device during ongoing resuscitation and/or patient transport. This is possibly more common with the i-gel SAD.
- Trauma to the patient's airway. This is likely to occur with similar frequency with both devices.
- Device failure. This is likely to occur with similar frequency with both devices.

Society will benefit from the evidence generated from this study, which will indicate the best initial airway management in OHCA. This will in turn benefit future OHCA patients in the UK and overseas, by reducing the risk of death and disability following OHCA, and potentially improving the use of healthcare resources.

9.4 Informing potential paramedics of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the paramedic PIL.

9.5 Obtaining informed consent from paramedics

Eligible paramedics will be sent an invitation letter, paramedic PIL and consent form. If the paramedic has any questions or concerns that they would like to raise, contact details of the study co-ordinator or local research paramedic will be provided in the paramedic PIL.

If individual paramedics are interested in participating in the study, they will be invited to attend a training session (see section 5.3.1), where generic training on resuscitation and the study procedures, including data collection, will take place and paramedics will also have the opportunity to ask any questions. At this point in the training session paramedics will be asked to provide written informed consent. Any paramedics who do not wish to consent to taking part in the study will be free to leave the training session at this point without prejudice.

Paramedics, who do consent, will be given a copy of their consent form to keep for their own records and the original will be retained for the study records. Paramedics consenting to the study will then be randomised to one of the two trial groups (i-gel or intubation) and the reminder of the training session will be trial group specific.

9.6 Informing potential study participants of possible benefits and known risks

At the point of consent, patients will have already received treatment for the cardiac arrest. There are no anticipated disadvantages or risks to participants consenting to the follow up phase of the study.

9.7 Obtaining informed consent from participants

When a cardiac arrest occurs it is not possible to obtain consent from the patient. Consent will be obtained retrospectively (deferred consent) if the patient survives to hospital admission and recovers sufficiently to be able to understand the study and its aims. If the patient does not survive consent will not be sought retrospectively.

The timing of the approach is important and needs to balance the need to inform at an early opportunity while determining accurately which patients have died, and which are potentially able to give consent. Consent will usually be obtained soon after discharge from ICU. A patient PIL will be

provided and written consent/assent obtained. Once written consent/assent has been obtained the patient's general practitioner will be sent an information letter detailing the study.

9.7.1 Consent process for surviving patients with capacity

All enrolled patients that survive to hospital admission will be followed-up by a member of hospital staff or a member of the research team, who will consult with clinical staff caring for that individual to determine the optimal time to approach the patient and/or their family to seek consent/assent for further follow-up and data collection. Ward-based clinical staff will also be asked to confirm that survivors have mental capacity before they are approached, and where necessary these clinical staff will introduce the study and research team members to patients.

All surviving potential participants will be given or sent a patient PIL, approved by the REC describing the study, and will be invited to participate in the follow-up phase.

Where possible, survivors will be approached whilst they are recovering. Usually, patients stay in the ICU or CCU for 2-5 days after their OHCA, following which they are transferred to a general medical ward. Our patient and public research advisory group has advised against approaching patients for consent whilst they are still on ICU/CCU since consent is not a time critical process, and has no impact upon the patient's treatment or care.

The individual taking consent will confirm the patient's eligibility, answer any questions and allow the patient a period of time to go over the PIL and consult others. They will then return at a later time, as guided by the patient but usually after at approximately 24 hours have elapsed, to take written informed consent if the patient decides to participate. The name and address of those who consent to active follow-up will be captured at this time.

There will be 3 different consent options:

A. The patient can consent to ACTIVE follow-up; where both routine data sources will be used and the patient will be actively followed up at discharge, 3 and 6 months after the index OHCA. Quality of life and mRS score will be collected at these time points.

B. The patient can consent to passive follow-up; with this option only routine data will be collected and the patient will not be contacted again about the study.

C. If a patient does not wish to be followed up they can select the option; I decline to take any further part in the study. I do not wish to be contacted again (with this option no further data collection will take place).

We will ask all OHCA survivors to sign the consent form, selecting which method of follow up they would prefer (three different options on the consent form).Patients will be given a copy of the consent form for their own records, one copy will be placed in the patient's medical records and the original copy will be kept in the secure study records.

If a patient does not wish to complete the consent form a record of this will be taken and these patients will automatically be assigned to option C where no further data collection will take place.

In the rare event of a patient with capacity being unable to physically complete the consent form, verbal consent will be accepted and will be documented on the study specific consent form and in the medical notes. An independent member of staff (e.g. a registered nurse caring for that patient) will be asked to annotate the consent form to indicate that they have witnessed verbal consent.

There will be a few cases where patients are discharged from hospital (either to another facility or their usual place of residence) before the consent process can be completed. We will post a PIL to these patients, with a covering letter, patient consent form. We will provide contact details of the local research nurse so that the patient can easily contact someone if they have any questions about the study.

If the patient wishes to participate, we will ask them to sign the consent form, keep one copy for their own records and we will ask for the other two copies to be returned in a prepaid envelope. If a patient fails to respond within 28-days of the information being sent we will assume that they do not consent to follow-up, and no further data will be collected.

9.7.2 Surviving patients who lack capacity

For patients lacking capacity (as assessed by the clinical staff caring for the patient on the ward) an opinion will be sought from a close relative or friend ("consultee"), who will be asked to provide advice about the patient's wishes and feelings, and whether they would wish to participate in the follow-up phase, according to the provisions of the Mental Capacity Act (2005). This personal consultee will also be identified by ward-based clinical staff caring for the patient, and these staff will introduce the study and local research team member to the prospective consultee as required. Modified PIL and response forms specifically designed for a consultee will be used. Any questions raised will be addressed by the research team.

If the identified individual agrees to act as a consultee we will ask them to sign the response form. The consultee will be asked to advise which method of follow up the patient would prefer (see section 9.7.1). On signing the response form, the consultee will be given a copy of the form to keep for their own records, a second copy will be placed in the patient's medical records and a third copy will be retained in a secure location by the study team.

If a patient without capacity is discharged from hospital (either to another facility or their usual place of residence) before the opinion of a personal consultee can be sought we will identify a personal consultee through communication with the clinical staff responsible for that patient's care whilst in hospital. The modified PIL and a response form will then be sent to the potential personal consultee with a covering letter. We will provide contact details for the consultee to get in touch with the study team so that they have an opportunity to ask any questions they may have.

If a personal consultee fails to respond within 28-days of the information being sent we will assume that the patient would not consent to follow-up, and no further data will be collected.

9.8 Co-enrolment

Because of the urgency of treatment there is no opportunity to identify whether a patient is already enrolled in a research study, and so it will be assumed that this is not the case*. Since the duration of intervention is very short it is highly unlikely that inadvertent co-enrolment will lead to any difficulties. Patients who have been enrolled in this study could be considered for co-enrolment in subsequent research (for example trials occurring in ICU), providing the combined follow-up procedures do not conflict, and are not considered unduly arduous. Participants may be enrolled in observational studies.

*The only exception to this would be where an attending paramedic may have already have enrolled the patient in another pre-hospital randomised trial; in these rare circumstances the patient will be excluded from taking part in the AIRWAYS-2 study.

10. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care
- The trial will be subject to the requirements of the Mental Capacity Act 2005.

10.1 Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.

10.2 NHS approval

Approval from the local NHS Trust (s) is required prior to the start of the trial.

Any amendments to the trial documents approved by the REC will be submitted to the Trust for information or approval as required.

10.3 Investigators' responsibilities

The local principal investigators situated within each of the ambulance will be required to ensure that local research approvals have been obtained by their ambulance trust and that any contractual agreements required have been signed off by all parties before recruiting any participant. They will be required to ensure compliance to the protocol and study manual throughout the duration of the study.

The local principal Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or CTEU Bristol or any regulatory authorities. They will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved the REC that they receive and ensure that the changes are complied with.

10.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor (or CTEU Bristol if they have been delegated to monitor see 7.2.2), the relevant REC and for inspection by other licensing bodies.

10.5 Indemnity

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

10.6 Clinical Trial Authorisation

The intervention is not classed as an investigational medicinal product as the I-gel device is CE marked and is being used with its license, therefore a Clinical Trial Authorisation from the MHRA is not required.

11. Data protection and participant confidentiality

11.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will be entered onto a purpose designed database and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

Access to the database will be via a secure password-protected web-interface (NHS clinical portal). Study data transferred electronically between the University of Bristol and the NHS will only be transferred via a secure NHS net network in an encrypted form.

Data from ambulance trust and receiving hospitals will be submitted to the CTEU Bristol either directly into the database which will be accessed by via the NHS portal or by secure fax or by recorded delivery.

11.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

Where trial related information is documented in the medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where the date is five years after the last patient last visit.

Access to stored information will be restricted to authorised personnel. Data forms will be stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data will be stored in a secure area of an NHS hospital server.

Any data that are transferred out of the secure environment (for example for statistical analysis) will be anonymised and individual participants identified by study number only.

In compliance with the Medical Research Policy (MRC) on Data Preservation, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and NHS number) will also be held until the study database has been locked, all data validated and the results from the study published. These identifiers will be held in a separate file and in a physically different location (NHS hospital server).

11.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.

12. Dissemination of findings

A dissemination strategy will be implemented that includes electronic dissemination of the study outputs to ambulance services in the UK and overseas, to acute trusts, and through a publicly accessible website. We will also feedback to all stakeholder groups and will present our findings at relevant conferences and at international ambulance, resuscitation and emergency care meetings.

Findings will be published in high-impact journals, presented at conferences, circulated in newsletters and will also be shared with international groups responsible for the generation of resuscitation guidelines (see below).

We will pay particular attention to dissemination to the public and ambulance services, since this is where the findings will be most readily implemented. In particular there will be important implications

for paramedic training and skills retention, and we will ensure that we make our training materials freely available for future adaptation and use.

Because resuscitation for OHCA is strongly protocol driven, we anticipate that the findings will be readily adopted into practice through changes to accepted guidelines. This will lead to tangible benefits to future OHCA patients, and may also benefit ambulance services by enabling rationalisation of training and equipment, as well as having the potential to prove cost effective for the NHS and society as a whole. We are therefore examining cost effectiveness as an integral component of this research.

13. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
Pre-ethical approval	1.0	01/08/2014	2.0	16/09/2014	Reference to a 12 month follow up has been removed, wording paramedic arrival change to 'at patient's side' rather than 'at scene'. Patient exclusion criteria updated to include opt-of trial. The Cognitive function using CPC has been removed. Data Collection; clarified that the screening log of all patients that have an OHCA should only include patients for whom resuscitation is attempted. The statistical analysis has been modified to account for retrospective exclusion	
2	2.0	08/01/2015	3.0	12/01/2015	Inclusion/exclusion criteria added (section 4.4.2), more detail added about 1°and 2° outcome (section 4.6.1), extra strata added to randomisation(Section 5.1), End of trial definition updated (section 5.5), Section 5.6.2 , 5.7, 5.11 & 6.5 details better defined.	
3	3.0	12/01/2015	4.0	13/04/2015	Inclusion/exclusion criteria modified (section 4.4.1 & 4.4.2), clarity added to primary outcome (section 4.6.1), section 5.3.2 the word quantitative has been removed when describing carbon dioxide monitoring. Section 6.5, reference to comparative costs of pre-registration training have been removed.	

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