AIRWAYS-2
Statistical Analysis Plan

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Effective Date:	

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List of abbreviations

Acronym	Details
AFT	Accelerated failure time
A2	AIRWAYS-2
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
CRF	Case report form
EAST	East of England ambulance service
ED	Emergency department
EMAS	East midlands ambulance service
EMS	Emergency Medical Services
ETCO2	End tidal carbon dioxide
HES	Hospital Episode Statistics
HR	Hazard ratio
ICU	Intensive care unit
IQR	Inter quartile range
ITT	Intention to treat
mRS	Modified rankin score
NHS	National Health Service
NPA	Nasopharyngeal airway
OHCA	Out of hospital cardiac arrest
OPA	Oropharyngeal airway
OR	Odds ratio
QoL	Quality of life
RCT	Randomised controlled trial
ROSC	Return of spontaneous circulation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SGA	Supraglottic airway device
SWAST	South western ambulance service
TR	Time ratio
YAS	Yorkshire ambulance service

1. INTRODUCTION TO SAP

1.1 Scope

This document details information regarding the statistical analysis of the completed AIRWAYS-2 (A2) trial and covers the analyses of the clinical outcomes outlined in the study protocol, with the exception of the health economic evaluation.

The plan is to report the primary outcome results as soon as data on the primary and secondary outcomes to hospital discharge or 30 days are available and report the longer term outcomes to 6 months subsequently. This will allow timely reporting of the primary results to coincide with a sister trial being conducted in the United States.

1.2 Editorial changes

Any changes made to this statistical analysis plan (SAP) after approval must be clearly justified and documented as an amendment at the end of this document. The SAP should then be re-approved.

1.3 SAP document approval

The statistical CTEU co-director should authorise this document.

1.4 Skeleton tables and figures

Throughout this document references are made to any skeleton tables and figures to be used in the reporting of the study (e.g. **Figure F1** or **Table T1**). Such tables and figures can be found in **Appendix A** of this document, and are intended as a guide for trial reporting. Final versions of the tables/figures may differ: tables may be combined, and/or their layout or numbering may differ. However the content should be consistent with **Appendix A.**

2. STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

AIRWAYS-2 is a randomised controlled trial (RCT) in four UK ambulance trusts (South Western Ambulance Service NHS Foundation Trust (SWAST), East of England Ambulance Service NHS Trust (EAST), East Midlands Ambulance Service NHS Trust (EMAS) and Yorkshire Ambulance Service NHS Trust (YAS)) with cluster randomisation at the paramedic level.

Two advanced airway management devices for the treatment of out of hospital cardiac arrests (OHCA) are compared: the i-gel, a second generation supraglottic airway device (SGA), and tracheal intubation, currently standard practice.

Ambulance staff performing the airway management are unable to be blinded to allocation but the patients and research staff assessing all outcomes post hospital admission (including the primary outcome) will be blinded.

2.2 Study objectives

1. To estimate the difference in the primary outcome of mRS at hospital discharge or 30 days post OHCA, whichever comes first, between groups of patients managed by paramedics randomised to use either the i-gel or intubation as their initial advanced 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 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. This objective will not be covered in this analysis.

2.3 Primary outcome

The primary outcome is mRS assessed at hospital discharge (or 30 days post OHCA if patient remains in hospital until this time). The mRS incorporates survival status and will be analysed as good recovery (scores 0 to 3) compared to poor recovery/death (scores 4 to 6).

2.4 Secondary outcomes

The protocol includes the secondary outcomes listed below (a health economic outcome is also listed in the protocol but excluded here).

All enrolled patients:

1. Initial ventilation success, defined as visible chest rise and end tidal carbon dioxide ($ETCO_2$) at the first or second attempt[1].
2. Regurgitation/aspiration.
3. Loss of a previously established airway.

[1] Note: chest rise and $ETCO_2$ is the definition on the CRF, but $ETCO_2$ is not included in the definition given in the protocol. Also, the protocol does not state whether success should be based on the first attempt only or the first or second attempt.

4. Actual sequence of airway interventions delivered.
5. Chest compression fraction (two ambulance regions only, added part way through the trial)
6. Return of spontaneous circulation (ROSC)*.
7. Airway management in place when first ROSC was achieved or the resuscitation was discontinued.

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

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

Patients who survive to hospital discharge and consent to active follow-up (estimated 9% of enrolled patients):

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

Patients who survive beyond hospital discharge and consent to active follow-up:

11. Time to death or last follow-up
12. Modified Rankin score at 3 and 6 months following OHCA
13. QoL (using the EQ-5D) at 3 and 6 months following OHCA.

* *note: this outcome includes both ROSC during advanced airway management attempts carried out by an Airways-2 paramedic and on ED arrival for those patients conveyed to ED*

2.5 Changes to the study objectives during the course of the study

N/A

2.6 Changes to the study outcomes during the course of the study

There have been no outcomes added or removed, but outcomes that were not clearly defined in the protocol have been reviewed and precise definitions have been agreed. These include definitions for secondary outcomes 1 to 7, the addition of time to death as a more informative means of comparing length of ICU and hospital stays and two analyses of survival at 72h (as binary and time to event outcomes). Definitions are given in Section 5.

3. STUDY POPULATION

The study population is patients aged 18 or over experiencing a non-traumatic OHCA. Enrolled patients must be attended by an A2 paramedic who is first or second at the patient's side and resuscitation must be commenced or continued by ambulance staff or responder. For specific inclusion/exclusion criteria and details of study patients and paramedics see template **Figures F1** and **F2**. 'Trial patients' are those who are resuscitated, attended by an A2 paramedic and meet the eligibility criteria.

Recruitment over time against targets will be presented by trust and overall (**Figures F3, F4 and F5**).

In the context of this trial, 'advanced airway management' refers to the use of intubation, the i-gel device or other supraglottic airway devices.

3.1 Consent

Due to the emergency nature of the trial, we have ethical approval to enrol patients without consent and seek consent for further participation from patients who survive to discharge from intensive care (ICU). We have approval to retain data collected up to the point of approach (or death if this occurs before approach) as well as mRS at hospital discharge or death for all patients regardless of whether they consent.

Patients may choose one of the following three options when presented with the trial information and consent form:

Active follow-up - Routine data will be utilised and the patient will be actively followed up at hospital discharge, and 3 and 6 months after the index OHCA. QoL and mRS will be collected at these three time points.

Passive follow-up - Only routine data will be collected and the patient will not be contacted again about the study.

Does not wish to participate – No further data collection will take place.

3.2 Flow of participants

Participant and paramedic flow will be described via flowcharts (see **Figures F1 and F2**). Follow-up will occur at three and six months post OHCA (target ±4 weeks) for patients who consent to active follow-up.

3.3 Characteristics of non-study patients

All resuscitated patients who are attended by an A2 paramedic and meet the eligibility criteria are automatically enrolled in the study and classed as trial patients. Key demography and initial cardiac arrest details are collected for all resuscitated patients, including those who are not attended by an A2 paramedic or are ineligible; these details will be described for trial and non-trial patients (**Table T1**). Resuscitated non-trial patients are referred to as population 0 in this document.

3.4 Randomisation

Paramedics are randomised (1:1 allocation) to either the i-gel or intubation group using an in-house internet-based system. Randomisation is stratified by ambulance trust, clinical experience (greater than or equal to 5 years full-time operational experience verses less than 5 years full-time operational experience) and the location of the paramedic's base ambulance station (greater than or equal to 5 miles verses less than 5 miles from the

nearest hospital with an emergency department that receives cardiac arrest patients; this is a proxy for urban vs. rural location).

To avoid bias that may be introduced by the cluster randomisation all patients who are resuscitated, attended by an A2 paramedic and meet the eligibility criteria are automatically enrolled in the trial and considered trial patients. If the attending paramedic forgets to treat a patient according to the A2 protocol or chooses not to follow the protocol, the patient is still enrolled in the trial and the attending A2 paramedic is still considered to be the enrolling paramedic and will be asked to complete a CRF; these patients are noted on the database as not 'consciously' enrolled and if they did not treat the patient according to their allocation will be counted as a protocol deviation (see section 3.5).

3.5 Protocol deviations

The following protocol deviations will be considered:

- A patient did not meet the study eligibility criteria but was consciously enrolled in the study by the attending A2 paramedic. This may occur because the paramedic believed the patient to be eligible at the time of treatment but later found out they were not. These patients are not considered to be 'trial patients' and will not be included in the study population, but such deviations will be noted.
- The wrong paramedic enrolled the patient. According to the A2 protocol, if a patient is eligible the first A2 paramedic on scene should enrol and treat the patient. Sometimes, due to reasons such as miscommunication, a second A2 paramedic may enrol and treat the patient instead. These patients will be analysed in the allocated intervention group of the *first A2* paramedic on scene.
- The enrolling A2 paramedic did not perform any advanced airway management but another paramedic did. This will mostly happen if the A2 paramedic forgets to enrol the patient (and they are therefore not 'consciously' enrolled) or due to space issues they allow another paramedic to treat the patient. Note. If no advanced airway management was required once the enrolling paramedic arrived (e.g. because ROSC had already occurred) this is not a deviation.
- The enrolling paramedic performed an alternative intervention to their allocation on their first advanced airway management attempt. According to the A2 protocol, enrolling paramedics should make two advanced airway management attempts with their allocated intervention before swapping to a different approach. The exception to this is solo responders in the intubation arm who are not allowed to intubate until another ambulance clinician arrives; occurrences of solo responders in the intubation arm using an i-gel before intubation will not count as a deviation but will count as a crossover in any as-treated analyses (see section 6.2.2. for details).
- The number of patients for whom the enrolling paramedic made only one attempt at their allocated intervention before swapping to an alternative advanced airway intervention will be noted. This is not considered a true protocol deviation as clinical reasons may have rendered a second attempt at the allocated intervention futile.

The number of patients who were not 'consciously' enrolled in the trial will also be noted. This will often be the reason for deviations such as a patient receiving the wrong intervention, but is not a deviation in its own right.

The frequency of each type of deviation will be tabulated by intervention allocation of the first A2 paramedic on scene (**Table T2 and Figure F6**). Note. It may be possible for patients to be classified as a protocol deviation for more than one reason.

3.6 Withdrawals

We have ethics approval to retain data collected up to the point of approach (after discharge from ICU) for all enrolled patients. However, patients who survive to ICU discharge and consent to participate in further data collection may later decide to withdraw. In some cases patients may be happy for data collection to continue, or for data collected up until withdrawal to be used, and therefore such patients will be included in the study analyses on an intention to treat basis (ITT). For patients who do not wish for their previously collected data to be used, we will exclude all data collected after the point of consent (i.e. ward movements, EQ-5D and follow-up data) from any analyses.

Data on all withdrawals is captured on a specific case report form (CRF), and will be tabulated by allocation of the enrolling paramedic (**Table T3**).

3.7 Analysis populations

- **Population 1a:** The analysis population for the primary outcome (mRS at discharge/30-days) is all patients who receive resuscitation, are attended by an A2 paramedic and meet the eligibility criteria, i.e. all trial patients. This is also the analysis population for outcome 5 (chest compression fraction), but limited to two trusts and starting partway through the trial.
- **Population 1b:** The analysis population for the second component of secondary outcome 6 (ROSC on ED arrival) is all patients who receive resuscitation, are attended by an A2 paramedic, meet the eligibility criteria and were conveyed to ED.
- **Population 2:** The analysis population for secondary outcomes 1 to 4, 6 and 7 (airway management details, but only covering ROSC during advanced airway management by A2 paramedic for outcome 6) is all trial patients who received at least one advanced airway management attempt by the enrolling A2 paramedic.
- **Population 3:** The analysis population for secondary outcome 8 (length of initial ICU stay) is all trial patients who were admitted to ICU.
- **Population 4:** The analysis population for secondary outcome 9 (length of hospital stay) is all trial patients admitted to hospital who did not refuse consent (i.e. patients who either consent to active or passive follow-up or who die prior to approach).
- **Population 5:** The analysis population for secondary outcomes 10 and 13 (EQ-5D heath scores and state scores) and secondary outcomes 11 and 12 (time to death after discharge and mRS during follow-up) is all trial patients who consent to active follow-up, survive to 30 days/hospital discharge and provide relevant data for at least one of the three time points (30 days/hospital discharge, 3 months and/or 6 months).
- **Population 0**: The population of patients who were resuscitated but did not become trial patients (either because they were not attended by an A2 paramedic or were ineligible). Characteristics of this population will be compared to those in population 1 (see **Table 1**).

The primary analysis will be performed on an ITT basis, with patients grouped by the allocation of their first A2 paramedic on scene (see section 6.2.2 for details).

3.8 Safety population

The safety population is all trial patients (cf. analysis population for the primary outcome). Only serious adverse events which are unexpected and related to the intervention are collected, so numbers are expected to be low. These will be presented along with all intervention details.

4. DATA SOURCES

A number of variables collected in AIRWAY-2 are recorded in more than one place. The following table details these variables and identifies the primary data sources and the order in which data will be selected; for example gender will be taken from Form G2, if not available from Form G2 then Form G will be used, if not available from Form G then Form E1 will be used and if not available from Form E1 then Form B will be used.

Variable	Data sources	Order of preference
Date and time of incident	Form A (CAD) Form E1 (paramedic)	Always use form A as this should be available for all patients
Gender	Form B (minimal dataset/CAD) Form E1 (paramedic) Form G (hospital details, only available for those surviving to hospital admission)	1. Form G2 2. Form G 3. Form E1 4. Form B
Date of birth (DOB)	Form B (minimal dataset/CAD) Form E1 (paramedic) Form G (hospital details, only available for those surviving to hospital admission)	1. Form G2 2. Form G 3. Form E1 4. Form B
Approximate age (Note. This variable will only be used if the date of birth is missing from all sources. If date of birth is recorded, age will be derived (see Section 5)	For patients who do not survive to hospital, age may be estimated on scene. If this is the case, this will be recorded on Form B (minimal dataset/CAD) Form E1 (paramedic)	1. Form E1 2. Form B
Presenting rhythm	Form B (minimal dataset/CAD) Form E1 (paramedic)	1. Form E1 2. Form B
Was event witnessed?	Form B (minimal dataset/CAD) Form E1 (paramedic)	1. Form E1 2. Form B
Who was the event witnessed by?	Form B (minimal dataset/CAD) Form E1 (paramedic)	1. Form E1 2. Form B
Was there bystander cardiopulmonary resuscitation (CPR)?	Form B (minimal dataset/CAD) Form E1 (paramedic)	1. Form E1 2. Form B
Date and time of hospital admission/emergency department (ED) admission	Form D (minimal dataset/paramedic contact) Form E1 (paramedic) Form G (hospital staff)	1. Form G 2. Form E1 3. Form D

5. DERIVATIONS

5.1 Primary outcome

To be calculated for all patients in population 1. Modified Rankin Score (0 to 6) at hospital discharge (or 30 days post-OHCA if the patient is still in hospital at that time) is recorded for all patients who survive to hospital discharge (or 30 days post-OHCA). All trial patients who do not survive to hospital discharge (or 30 days post-OHCA) will be assigned a score of 6 (dead). mRS will be dichotomised and analysed as good recovery (score 0 to 3) compared to bad recovery/death (score 4 to 6).

Note. mRS is also collected at 3 and 6 months post-OHCA for patients who consent to active follow-up and will be used to calculate a dichotomised score as above and utilised for the secondary outcome of mRS up to 6 months. Patients who are known to have died post hospital discharge will be given a score of 6. This will be ascertained from both data collected during the course of the trial and HES data sent by NHS digital.

5.2 Compression Fraction

The compression fraction (expressed as a percentage) is measured by placing a credit-card-sized CPRCard device (Laerdal Medical,Stavanger, Norway) on the patient's chest during CPR to collect chest compression data. Data are downloaded from the card and interpreted using a CPRCard Laerdal Card reader ID CPR30-LA (FEIG Electronic, Germany) and a standard algorithm.

5.3 EQ-5D

To be calculated for all patients in population 5 at up to three time points: hospital discharge/30days post OHCA, 3 months post OHCA and 6 months post OHCA.

A five digit 'state' score will be derived from the mobility, self-care, usual activities, pain/discomfort and anxiety/depression scores using the following:

State = 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score

Each state will then be assigned a single summary index score according to a standard scale. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health. If any of the five raw scores are missing, the state score and index score will be missing.

The EQ-5D questionnaire visual analogue scales are also collected. Such scores range from 0 to 100 (with higher scores denoting higher QoL).

Trial patients who did not survive to 30 days/hospital discharge will be assigned EQ-5D visual analogue scale and summary index scores of zero. Trial patients who survived to hospital discharge but died prior to their 3-month follow-up will be assigned 3-month and 6-month follow-up EQ-5D visual analogue scale and summary index scores of zero. Trial patients who survived to 3-month follow-up but died prior to their 6-month follow-up will be assigned 6-month follow-up EQ-5D visual analogue scale and summary index scores of zero. The survival statuses of the patients will be ascertained using data collected during the course of the trial as well as from HES sent by NHS digital.

5.4 Other variables

New variable	Rules
POPULATION 0 and 1:	
Age	If date of birth ≠ missing: Age= (OHCA date – Date of birth) /365.25 If date of birth = missing: Age= approximate age (see section 4) Else missing
999 call to first crew arrival time (mins)	(First crew arrival date-incident date)*24*60 + (First crew arrival time-incident time)
POPULATION 1:	
Trial patient	If was resuscitation attempted=Yes and was incident attended by Airways-2 paramedic=Yes and did patient meet eligibility criteria=Yes, then = Yes If was resuscitation attempted=No or was incident attended by Airways-2 paramedic=No or did patient meet eligibility criteria=No, then = No Else missing
Survival status to hospital discharge	If admitted to ED (Form D)=No, then = Died on scene If admitted to ED=Yes, and survived to ICU admission (Form G)=No, then = Died prior to ICU admission If admitted to ED=Yes, and survived to ICU admission=Yes, and survived to ICU discharge (Form G)=No, then = Died prior to ICU discharge If admitted to ED=Yes, and survived to ICU admission=Yes, and survived to ICU discharge (Form G)=Yes, and transferred=Yes and level of care in transferred hospital (form G2)=Level 3 and survived to ICU discharge (Form G2)= No, then = Died prior to ICU discharge If admitted to ED=Yes, and survived to ICU admission=Yes, and survived to ICU discharge=Yes and ((transferred = No) or (transferred=Yes and level of care admitted to is level 2 or 1) or (transferred=Yes and level of care admitted to is level 3 and survived to ICU discharge=Yes)) and (mRS (Form H2/I2)=6 or (mRS (Form H2/I2) ≠6 & has patient died since ICU discharge (but prior to hospital discharge) (Form W2) = Yes) or survived to hospital discharge (form H3/I3)=No), then = Died prior to hospital discharge If admitted to ED=Yes, and survived to ICU admission=Yes, and survived to ICU discharge=Yes and ((transferred = No) or (transferred=Yes and level of care admitted to is level 2 or 1) or (transferred=Yes and level of care admitted to is level 3 and survived to ICU discharge=Yes)) and (mRS≠6 or survived to hospital discharge=Yes, then = Survived to 30 days/hospital discharge)
Date of death	If survival status=died on scene, then = Date resus stopped (Form E1) If survival status=died prior to ICU admission, then = Date of death 1 (Form G) If survival status=died prior to ICU discharge and survived to ICU discharge (Form G)=No, then = Date of death 2 (Form G)

New variable	Rules
	If survival status=died prior to ICU discharge and survived to ICU discharge (Form G2)=No, then = Date of death 3 (Form G2) If survival status=died prior to hospital discharge & consent status=active or passive, then = death date (Form H/I3) If survival status=died prior to hospital discharge & consent status≠active & consent status≠passive, then = death2 date (Form W2) If survival status=survived to 30 days/hospital discharge & has patient died since hospital discharge=Yes, then = death3 date (Form W2) Else missing
Time of death	If survival status=died on scene, then = Time resus stopped (Form E1) If survival status=died prior to ICU admission, then = Time of death 1 (Form G) If survival status=died prior to ICU discharge and survived to ICU discharge (Form G)=No, then = Time of death 2 (Form G) If survival status=died prior to ICU discharge and survived to ICU discharge (Form G2)=No, then = Time of death 3 (Form G2) If survival status=died prior to hospital discharge & consent status=active or passive, then = Time of death (Form H/I3) If survival status=died prior to hospital discharge & consent status≠active and status≠passive, then = 12 midnight If survival status=survived to 30 days/hospital discharge & has patient died since hospital discharge=Yes, then = 12 midnight (we do not collect time of death for patients who died after ICU discharge and do not consent to any follow-up or for patients who consent to active follow-up but died after hospital discharge) Else missing
Time to death	*For patients who die prior to admission, in hospital, or during the follow up period:* (Date of death – Incident date (Form A))*24*60 + (Time of death – Incident time (Form A)) *For patients who survive to 30 days/hospital discharge & consent to active follow-up and provides 6 month follow-up data (i.e. censored at 6 months post discharge for analysis)=* (6m follow-up date (Form K-Cover) - Incident date (Form A)) *24*60 + (12 midday - Incident time (Form A)) *For patients who survive to 30 days/hospital discharge & consent to active follow-up and provides 3 month follow-up data but not 6 month follow-up data (i.e. censored at 3 months post discharge for analysis)=* (3m follow-up date (Form K-Cover) - Incident date (Form A)) *24*60 + (12 midday - Incident time (Form A)) *For patients who survive to 30 days/hospital discharge & consent to passive follow-up or consented to active follow-up but do not provide any 3 or 6 month data (i.e. censored at hospital discharge for analysis)=* (Hospital discharge date (Form H/I3) - Incident date (Form A)) *24*60 + (Hospital discharge time (Form H/I3) - Incident time (Form A))

New variable	Rules
	For patients who survive to (30 days or) hospital discharge & did not consent to active or passive follow-up (i.e. censored at ICU discharge for analysis) = (ICU discharge date (Form G) - Incident date (Form A)) *24*60 + (ICU discharge time Form G) - Incident time (Form A)) *Note – if time to death exceeds 183 days, then it will be censored at 183 days*
Time to death event/censor variable	If (survival status≠survived to 30 days/hospital discharge & survival status≠missing) or has patient died since hospital discharge=Yes, then = 0 If survival status=survived to 30 days/hospital discharge & (has patient died since hospital discharge=No or missing), then = 1 Else missing *Note – if time to death exceeds 183 days, then it will be censored at 183 days*
72 hour survival	if time to death≥72 hours, then = Yes if time to death<72 hours & time to death censor variable=0, then = No if time to death<72 hours & time to death censor variable=1 & (mRS date-incident date) >3 & mRS at 30 days/discharge≠6, then = Yes Else missing
Time to death: 0 to 72h	if time to death≥72 hours, then = 72h if time to death <72 hours, then = time to death Else missing
Time to death event/censor variable: 0 to 72h	if time to death≥72 hours, then = 1 if time to death<72 hours & time to death censor variable=0 (patient died), then = 0 if time to death<72 hours & time to death censor variable=1 (censored), then = 1 Else missing
First crew arrival to first A2 paramedic arrival (mins)	(First A2 arrival date - First crew arrival date)*24*60 + (First A2 arrival time - First crew arrival time)
Time of 999 call to first A2 paramedic arrival (mins)	(First A2 arrival date - Incident date)*24*60 + (First A2 arrival time - Incident time)
Time between incident and discharge/30 day mRS measurement (days)	(mRS date-incident date) if measured face-to-face Else missing
Event witnessed by	if event witnessed by = non-ambulance staff (Form E1) or (event witnessed by =missing (Form E1) and event witnessed by = bystander (Form B)), then = bystander If event witnessed by = Airways-2 paramedic or ambulance staff (Form E1) or (event witnessed by = missing (Form E1) and event witnessed by = EMS (Form B)), then = EMS Else missing
Event witnessed by ambulance staff	If event witnessed by = EMS, then =Yes If event witnessed by = bystander, then =No If event was not witnessed, then =No

New variable	Rules
	Else missing
Utstein comparator group	if event witnessed by = bystander and presenting rhythm = VF or pulseless VT, then =Yes
	if (event witnessed by = bystander and presenting rhythm = Asystole OR PEA OR unknown) or event witnessed by = EMS, then =No
	if event witnessed = No, then =No
	Else missing
Protocol deviation 1: consciously enrolled but ineligible	if consciously enrolled=Yes AND trial patient=No, then =Yes
	if trial patient=Yes, then =No
	Else missing
Protocol deviation 2: wrong paramedic enrolling patient	if Paramedic Airways-2 ID (Form A)≠Paramedic Airways-2 ID (Form E1) and Paramedic Airways-2 ID (Form E1) ≠missing and trial patient=Yes, then =Yes
	if Paramedic Airways-2 ID (Form A)=Paramedic Airways-2 ID (Form E1) and Paramedic Airways-2 ID (Form E1) ≠missing and trial patient=Yes, then =No
Protocol deviation 2: wrong paramedic enrolling patient resulting in allocation crossover	if protocol deviation 2 = Yes and allocation of enrolling paramedic≠allocation of first A2 paramedic on scene, then =Yes
	if protocol deviation 2 = Yes and allocation of enrolling paramedic=allocation of first A2 paramedic on scene, then =No
	Else missing
Protocol deviation 3:	if 'If no [airways management attempt completed on CRF E2], why?' = Further airway management commenced once A2 paramedic arrived but not carried out by enrolling A2 paramedic and trial patient=Yes, then =Yes
	if 'has at least one airway management attempt recorded on CRF E2?'≠missing and 'If no [airways management attempt completed on CRF E2], why?' ≠ Further airway management commenced once A2 paramedic arrived but not carried out by enrolling A2 paramedic and trial patient=Yes, then =No
	Else missing
Protocol deviation 4	if (Paramedic allocated to i-gel and first advanced airways management attempt is intubation or other SGA) or
	(Paramedic allocated to intubation and first advanced airways management attempt is i-gel or other SGA and paramedic is not a solo responder), then =Yes
	if first advanced airway management attempt matches paramedic allocation, then =No
	Else missing (including patients with no advanced airways management attempts)
Protocol deviation 5	if (paramedic allocated to i-gel and number of i-gel attempts made before switching to intubation or other SGA=1 or (paramedic allocated to intubation and number of intubation attempts made before switching to i-gel or other SGA=1), then =Yes

New variable	Rules
	if (paramedic allocated to i-gel and number of i-gel attempts made before switching to intubation or other SGA≠ 1 and at least one advanced airways management attempt recorded) or (paramedic allocated to intubation and number of intubation attempts made before switching to i-gel or other SGA≠ 1 and at least one advanced airways management attempt recorded), then = No Else missing
POPULATION 2:	
Initial ventilation success in first or second attempt	If i-gel is used before intubation or other SGA: If ventilation success= yes on first i-gel attempt, then = Yes If ventilation success = no on the first i-gel attempt and the next advanced attempt is also i-gel and on that attempt ventilation success = yes, then = Yes If ventilation success = no on first i-gel attempt and the next advanced attempt is also i-gel and ventilation success = no, then = No If ventilation success = no on first i-gel attempt and (there is no further attempt or the next advanced attempt is intubation or other SGA), then = No If intubation is used before i-gel or other SGA: If ventilation success= yes on first intubation attempt, then = Yes If ventilation success = no on the first intubation attempt and the next advanced attempt is also intubation and on that attempt ventilation success = yes, then = Yes If ventilation success = no on first intubation attempt and the next advanced attempt is also intubation and ventilation success = no, then = No If ventilation success = no on first intubation attempt and (there is no further attempt or the next advanced attempt is i-gel or other SGA), then = No If other SGA is used before i-gel or intubation: If ventilation success= yes on first other SGA attempt, then = Yes If ventilation success = no on the first other SGA attempt and the next advanced attempt is also other SGA and on that attempt ventilation success = yes, then = Yes If ventilation success = no on first other SGA attempt and the next advanced attempt is also other SGA and ventilation success = no, then = No If ventilation success = no on first other SGA attempt and (there is no further attempt or the next advanced attempt is i-gel or intubation), then = No If advanced airway management is not used, then =Yes Else missing
Any ventilation success	If ventilation success=Yes for any advanced airway management attempts on Form E2, then = Yes If ventilation success=No for all advanced airway management attempts on Form E2, then = No

New variable	Rules
	Else missing
Any loss of previously established airway *(only calculated if any ventilation success=Yes)*	If 'if an airways was established, was it later lost'=Yes for any advanced airway management attempts on Form E2, then = Yes If ('if an airways was established, was it later lost'=No OR 'ventilation success'=No) for all advanced airway management attempts on Form E2, then = No Else missing
Actual sequence of airway interventions delivered	If at least one airway management attempted:- A six digit code will be derived from the airway management type (1=OPA, 2=NPA, 3=i-gel, 4=intubation, 5=other SGA, 6=other) used at the first to the 6th airway management attempt, using the following: Code = 100000*1st attempt airway management type + 10000*2nd attempt airway management type + 1000*3rd attempt airway management type + 100*4th attempt airway management type + 10*5th attempt airway management type + *6th attempt airway management type If no airways management attempted, = missing
Any ROSC during airway management	If 'was ROSC achieved'=Yes for any advanced airway management attempts on Form E2, then = Yes If 'was ROSC achieved'=No for all advanced airway management attempts on Form E2, then = No Else missing

Airway management in place when first ROSC was achieved or the resuscitation was discontinued if no ROSC was achieved	if ('any ROSC achieved during airway management'=Yes and airway management first time ROSC was achieved=intubation) OR ('any ROSC achieved during airway management'=No and final airway attempt= intubation and 'was airway management handed over'=No), then = intubation
	if ('any ROSC achieved during airway management'=Yes and airway management first time ROSC was achieved= i-gel) OR ('any ROSC achieved during airway management'=No and final airway attempt= i-gel and 'was airway management handed over'=No), then = i-gel
	if ('any ROSC achieved during airway management'=Yes and airway management first time ROSC was achieved= any SGA) OR ('any ROSC achieved during airway management'=No and final airway attempt= any SGA and 'was airway management handed over'=No), then = other SGA
	if ('any ROSC achieved during airway management'=Yes and airway management first time ROSC was achieved=OPA/NPA) OR ('any ROSC achieved during airway management'=No and final airway attempt= OPA/NPA and 'was airway management handed over'=No), then = other
	Else missing

Regurgitation	If regurgitation before advanced airway management on form E11 = Yes or regurgitation during/after advanced airway management on form E1 = Yes, then =Yes

New variable	Rules
	If regurgitation before advanced airway management on form E1 = No and regurgitation during/after advanced airway management on form E1 = No, then =No If advanced airway management is not used and regurgitation =missing, then =No Else missing
Aspiration	If aspiration before advanced airway management on form E1 = Yes or aspiration during/after advanced airway management on form E1 = Yes, then =Yes If aspiration before advanced airway management on form E1 = No or aspiration during/after advanced airway management on form E1 = No, then =No If advanced airway management is not used and aspiration =missing, then =No Else missing
POPULATION 3:	
Duration of initial ICU stay	*For patients who survive to ICU discharge in admitting hospital and (were not transferred or were transferred to another hospital but at a lower level of care)* = (ICU discharge date - ICU admission date)*24*60 + (ICU discharge time - ICU admission time) *For patients who are transferred from ICU in the admitting hospital to ICU (level 3 care) in another hospital and survives to ICU discharge in the transferred hospital* = ((ICU discharge date on Form G2 - ICU admission date on Form G)*24*60 + (ICU discharge time on Form G2- ICU admission time on form G)) *For patients who die in ICU in the admitting hospital (i.e. censored for analysis)* = (ICU death date - ICU admission date)*24*60 + (ICU death time - ICU admission time) *For patients who are transferred from ICU in the admitting hospital to ICU (level 3 care) in another hospital and die in ICU in the transferred hospital (i.e. censored for analysis)* = ((ICU death date on form G2 - ICU admission date on form G)*24*60 + (ICU death time on form G2 - ICU admission time on form G))
ICU duration event/censor variable	If survived to ICU discharge =Yes and transferred= No on form G, then = 1 If survived to ICU discharge =Yes and transferred= Yes on form G and survived to ICU discharge =Yes on form G2, then = 1 If survived to ICU discharge=No on form G, then = 0 If survived to ICU discharge =Yes and transferred= Yes on form G and survived to ICU discharge =No on form G2, then = 0 Else missing

New variable	Rules
ROSC on ED admission	If patient survived to ED/hospital admission then = ROSC on ED admission on form E1 If survival status = Died on scene, then =No Else missing
POPULATION 4:	
Duration of hospital stay	If survival status = survived to 30 days/hospital discharge and consent=active or consent=passive, then = (Hospital discharge date (Form H/I3) - ED admission date (Form G)) *24*60 + (Hospital discharge time (Form H/I3) - ED admission time (Form G)) If survival status= died prior to ICU admission or survival status= died prior to ICU discharge or (survival status=died prior to hospital discharge & ((consent status=active or passive) or patient was not approached)), then = (Date of death - ED admission date (Form G)) *24*60 + (Time of death - ED admission time (Form G)) Else missing
Hospital duration event/censor variable	If survival status =survived to 30 days/ hospital discharge and consent=active or consent=passive, then = 1 If survival status= died prior to ICU admission or survival status= died prior to ICU discharge or (survival status=died prior to hospital discharge & ((consent status=active or passive) or patient was not approached)), then = 0 Else missing
Timing of (patient) withdrawal	if date of withdrawal from study < date of discharge, then = pre-discharge if date of withdrawal from study > date of discharge, then = post-discharge Else missing
Decision taken by	if healthcare professional's decision=Yes and (patient choice = No or missing), then = health care professional if healthcare professional's decision=No or missing and patient choice = Yes, then = patient Else missing

6. STATISTICAL ANALYSES

6.1 Baseline data

Baseline characteristics (i.e. patient demography and initial cardiac arrest details) will be described grouped by the allocation of the first A2 paramedic on scene for all trial patients (see **Table T4**). Intervention details will also be described for all trial patients (see **Table T5**).

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. The summary statistic headings given in **Tables T4** and **T5** are those we expect to use based on a-priori knowledge of the clinical measurements gained from previous studies. However, if distributional assumptions are not satisfied, changes will be made.

Statistical tests to compare data not listed as outcomes will not be performed. Secondary outcomes 4 (sequence of airway interventions delivered) and 7 (airway management in place when ROSC was achieved or resuscitation discontinued) will be described but not formally compared.

6.2 Primary and secondary outcome data

6.2.1 Adjustment in models

The intention is to adjust the models for the three stratification (design) factors: ambulance trust (four levels), clinical experience (two levels) and the location of the paramedic's base ambulance station (two levels) as fixed effects, and paramedic as a random effect (or a shared frailty term in the time to event model). For the mRS model where the majority of patients will have a poor outcome/death, the data may be insufficient to allow estimation of regression coefficients for all these variables. If this is the case, inestimable stratification variables will be dropped from the model and will be noted in a footnote. For the time to death model, if a cox model is used the analysis will be stratified by trust (to allow for varying baseline hazards) and adjusted for the other design factors. If either of the design factors do not meet the proportional hazards assumptions, stratification by these factors will also be implemented.

6.2.2 Data presentation and analysis models

For intention to treat analyses, data will be presented and analysed by the allocated group of the first A2 paramedic on scene, regardless of what airway management the patient received. For as-treated analyses (see sections 6.2.5 and 6.2.6), data will be presented and analysed by the allocation of the first advanced airway management used; if neither i-gel nor intubation was used (or if another SGA was used before an i-gel or intubation), the patients will be excluded from as-treated analyses.

All analyses and data presentation will be by intention to treat unless otherwise stated in the Table heading.

All outcomes listed in Sections 2.3 and 2.4 will be presented as per the template tables **Table T6** to **T8** and may also be presented graphically. General methods of presentation and assessing intervention effects are outlined below. For formal comparisons the intubation group will be the reference group. Details specific to each outcome are described as appropriate. Secondary outcomes 10 to 13 will not be reported in the primary outcome paper.

Date type	Outcomes
Binary	mRS (at discharge/30days) Initial ventilation success Regurgitation/aspiration Loss of previously established airway Return of spontaneous circulation (ROSC) 72h survival
Categorical	Actual sequence of airway interventions delivered[1] Airway management in place when ROSC was achieved or resuscitation was discontinued or intervention from A2 paramedic stopped[1]
Continuous	Chest compression fraction Duration of ICU stay (presented separately for survivors and patients who die during ICU stay)[1] Duration of hospital stay (presented separately for survivors and patients who die during hospital stay) [1]
Time to event	Time from OHCA to when discharge/30 day mRS was assessed[1,3] Time to death[2] Time to death (up to 72h)
Longitudinal	mRS (at discharge/30days, 3 months and 6 months) EQ-5D index score and visual analogue scale score (at discharge, 3 months and 6 months)

Note:-

[1] These outcomes will be described but not formally compared

[2] Time to death will be formally compared in place of length of ICU and hospital stay

[3] This is not a specified outcome but the DMSC raised it as a point of interest.

- **Binary outcomes** will be presented as numbers and percentages of patients in the category of interest. Outcomes will be compared between intervention groups using logistic regression. The intervention comparison estimate will be presented as an adjusted odds ratio (OR) with a 95% confidence interval (95% CI) and p-value. Adjusted estimates of the risk difference and risk ratio with a 95% CI and p-value will also be calculated from a generalised linear model (risk difference, binomial family with identity link, risk ratio poisson family with log link) with standard errors adjusted for clustering (clustered sandwich estimator). Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome (with at least one event in each treatment group).
- **Categorical outcomes** will be presented as numbers and percentages of patients in each category. Outcomes will be compared between intervention groups using multinomial logistic regression. Treatment comparison estimates will be presented as adjusted odds ratios (OR) and 95% confidence intervals (95% CI).
- **Continuous outcomes** will be summarised by means and SDs in each treatment group, if distributions are approximately normal. If distributions are non-normal data will be summarised by the median and IQR or geometric mean (GM) if a logarithmic transformation provides an approximately normal distribution. Outcomes will be compared using linear regression. For untransformed data treatment comparisons will be presented as adjusted differences in means with 95% CI, and for logarithmically transformed data as adjusted ratios of GMs with 95% CI. Due to the large numbers of

trial patients not expected to survive to 30 days/hospital discharge, a two-part zero-inflated modelling approach will also be considered for EQ5D visual analogue scale and summary index scores. This will comprise a) an occurrence model, a logistic regression model for the occurrence of death vs survival; b) intensity model, a log-linear model for the score, conditional on survival. If the log-linear model for the score is a poor fit to the data, then a beta model for the score, will be considered. This requires a transformation of:

$$y' = (y - a)/(b - a)$$

$$y_n = [y'(N-1) + 1/2]/N$$

Where y is the untransformed score, a is the lowest possible value of the outcome, b is the highest possible value of the outcome and N is ????. For EQ5D index score a=-0.594 and b=1; and for EQ5D visual analogue scale a=0 and b=100. If the beta model for the score is a poor fit to the data, then a multilevel ordered logistic regression analyses using categorized EQ5D scores will be performed. Cut-offs will be based on those used in previous studies [1,2].

- **Time to event outcome** time to death will be summarised by the median and IQR in each intervention group. This will be compared using Cox's proportional hazards or parametric models as appropriate. The choice of model to use will depend on the distribution of the data. The intervention comparison will be presented as a hazard ratio (HR) and 95% CI if a proportional hazards model is used or time ratios (TR) and 95% CI if an accelerated failure time (AFT) model is used. Times will be censored according to the derivations in section 5.4.
- **Longitudinal outcomes** will be summarised for each time point. Binary and continuous outcomes will be compared using logistic and linear mixed effects methodologies (see continuous outcomes above) respectively, with the treatment group and study design variables (see section 6.2.1) fitted as fixed effects, and patient terms as random effects. If a time x treatment interaction is not statistically significant at the 10% level an overall treatment effect will be reported. If the interaction is statistically significant the changes in treatment effect with time will be described. Different variance/covariance structures will be explored, and the structure that provides the best fit in terms of information criteria such as AIC, BIC and likelihood ratio tests will be used.

6.2.3 Statistical significance

For hypothesis tests two-tailed p-values<0.05 are considered statistically significant.

6.2.4 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods, e.g. residual plots, tests for proportional hazards, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses and comments made in footnotes.

6.2.5 Subgroup analyses

Two subgroup analyses for the primary outcome are specified in the protocol: Utstein comparator group vs non-comparator group and arrest witnessed by ambulance staff or not (**Figure F7**).

Due to concerns regarding ventilation success raised during the trial, a subgroup analysis of the primary outcome comparing patients whose i-gel or intubation airway management attempt(s) were or were not 'successful' during the first and/or second attempt (see section 5.2 for definition) will also be performed. This analysis will be performed as-treated and as such will only include patients who received at least one advanced airway management attempt using an i-gel and/or intubation tube.

Subgroup effects will be fitted by adding a "sub-group x intervention" interaction term to the analysis model.

6.2.6 Sensitivity analyses

For the primary outcome, the following sensitivity analyses will be performed:

- ITT analysis including only patients who received at least one advanced airway management attempt using an i-gel and/or intubation tube.
- As-treated analysis including only patients who received at least one advanced airway management attempt using an i-gel and/or intubation tube (see section 6.2.5 for additional sub-group analysis for this outcome).
- ITT analysis including all patients who were attended by an Airways-2 paramedic but not resuscitated.

For the QoL secondary outcomes (EQ5D visual analogue scale (VAS) and index score) and longitudinal mRS, the following analyses will be performed:

- 'Worst case scenario' ITT analyses, where the following rules apply:
    - Patients who are known to have survived to 6 months post-cardiac arrest (from data obtained through HES or collected during the trial):
        - If patients have missing QoL or mRS data at any one of the 30 days post-/hospital discharge (whichever happens earlier), 3 months post-, or 6 months post-cardiac arrest, then these patients will be given 'worst possible' scores (the lowest score that can be recorded without being recorded as 'dead') where missing.
    - Patients who are known to have survived to 3 months post-cardiac arrest (from data obtained through HES or collected during the trial), but not known to have survived to 6 months post-cardiac arrest (likewise with missing data for all QoL and mRS data at 6 months post-cardiac arrest):
        - These patients will be given a score equivalent to 'dead' (0 for EQ5D VAS and index score, and 6 for mRS) at 6 months post-cardiac arrest.
        - If patients have missing QoL or mRS data at any one of the 30 days post-/hospital discharge (whichever happens earlier), or 3 months post-cardiac arrest, then these patients will be given 'worst possible' scores (the lowest score that can be recorded without being recorded as 'dead') where missing.
    - Patients who are known to have survived to 30 days/hospital discharge (whichever happens earlier) (from data obtained through HES or collected during the trial), but not known to have survived to 3 months post-, or 6 months post-cardiac arrest (likewise with missing data for all QoL and mRS data at 3 months post- and 6 months post-cardiac arrest):
        - These patients will be given a score equivalent to 'dead' (0 for EQ5D VAS and index score, and 6 for mRS) at 3 months post- and 6 months post-cardiac arrest.
        - If patients have missing QoL or mRS data at any one of the 30 days

post-cardiac arrest/hospital discharge (whichever happens earlier), then these patients will be given the 'worst possible' scores (the lowest score that can be recorded without being recorded as 'dead') where missing.

- 'Multiple imputed case scenario' ITT analyses, where the following rules apply:
  - Patients who are known to have survived to 30 days post-cardiac arrest/hospital discharge (whichever happens earlier) (from data obtained through HES or collected during the trial), but have missing data for any QoL or mRS outcomes at any of the 30 days post-/hospital discharge (whichever happens earlier), 3 months post-, and 6 months post-cardiac arrest timepoints, will be multiple imputed where: missing and where survival status (at least up to 30 days post-cardiac arrest/hospital discharge (whichever happens earlier)) is known. The following details specify the model that will be fitted for this scenario:
    - The multiple imputation model will be restricted to patients who have survived to the relevant follow-up timepoint (in order to not impute scores equivalent to 'dead'), for all QoL and mRS outcomes at:
      - 30 days post-cardiac arrest/hospital discharge (whichever happens earlier), the imputation model will be restricted to patients who did not die prior to 30 days post-cardiac arrest/hospital discharge
      - 3 months post-cardiac arrest, the imputation model will be restricted to patients who did not die prior to 3 months post-cardiac arrest
      - 6 months post-cardiac arrest, the imputation model will be restricted to patients who did not die prior to 6 months post-cardiac arrest
    - The variables to be included in the multiple imputation model will be: age; sex; length of ICU stay; treatment group; trust; paramedic experience; distance from paramedic's base ambulance station; and QoL and mRS scores at 30 days post-/hospital discharge (whichever happens earlier), 3 months post-, and 6 months post-cardiac arrest. Predictive mean matching will be used for continuous variables.
    - The percentage of missing data will be calculated for patients who survived to 30 days post-cardiac arrest/hospital discharge (whichever happens earlier) for all QoL and mRS outcomes and timepoints in turn. The number of imputations carried out will be the percentage value (rounded to the nearest 5) of the highest of these percentages.
    - The pooled estimates will be reported.

6.2.7 Missing data

In all tables missing data will be indicated by footnotes. If the amount of missing data differs substantially between treatment groups potential reasons will be explored.

Missing predictors:

There will be no missing data for any of the randomisation factors (by design).

Missing outcomes:

- If the proportion of missing data is less than 5% then complete case analysis will be performed (i.e. excluding cases with missing data).
- If the proportion of missing data is above 5% multiple imputation methods will be considered. A general imputation model that uses an iterative procedure to generate imputed values will be used to generate multiple complete data sets (e.g. using Stata's mi impute). The model of interest will be the fitted to each of the complete data sets and effect estimates combined using Rubin's rules.

If appropriate (the level of missingness is >20%) then any variables that are predictive of missingness will be identified, and if there is reason to suggest that an assumption of missing at random (MAR) given these variables is reasonable then such variables will be adjusted for in the models of interest. These models can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.

6.2.8 Multiple testing

No formal adjustment will be made for multiple testing. However as previously described formal statistical comparisons will not be made for outcomes with low event rates and only pre-specified subgroup analyses will be performed. Consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

6.3 Safety data

Safety data are only collected for events which are unexpected and potentially related to the intervention. All such events will be detailed along with descriptions of patients' airway management pathway. **Table T9** summarises such events, as captured via serious adverse event (SAE) report forms and full details will also be given as listings (see **Table T10**).

No formal comparisons between groups will be made as numbers of events are expected to be small.

7. AMENDMENTS TO THE SAP

Previous version	Previous date	New version	New date	Brief summary of changes
V1.0	14/02/2018	V2.0	14/04/2018	Clarified definition of enrolling paramedic to better reflect the protocol and how it is defined in the analysis code – rephrased as “first A2 paramedic on scene” throughout. Corrected typographical errors and updated figure numbers as a figure added to aid interpretation of the data (new Figure F6). Changed ‘Incident (999 call) to first crew arrival (mins)’ to ‘999 call to first crew arrival (mins)’ throughout at the suggestion of the DMSC and TSC. Corrected inconsistent naming of survival status in data derivations. Added new variable ‘Time of 999 call to first A2 paramedic arrival (mins)’ at the suggestion of the DMSC and TSC (Table T4). Added a sentence to clarify what will be reported in the primary outcome paper. For the analysis of the EQ-5D outcomes the following was added ‘If it is not possible to fit the model, then an analysis restricted to those who survive to hospital discharge will be considered.’ to the allow for the fact that the two part model may not be estimable due to the high proportion of deaths. Labelling of tables was clarified and errors in labelling data types (viz. n/% vs. mean/SD or median /IQR) corrected.

				Figure F1 was revised to improve readability at the suggestion of the DMSC and TSC. A skeleton footnote was added to the revised figure. Added a breakdown of the numbers by group (rather than Trust) in Figure F2. Added a category to the list of reasons for non-approach. Revised Table T1 to increase readability – information presented in column with no descriptive data available was moved to a footnote. Merged the columns 'Resuscitation attempted, attended by A2, but not eligible' 'trial patients' at the suggestion of the DMSC and TSC. Removed 'Enrolling paramedic made only one attempt at allocated intervention before swapping' from Table T2 as this is not considered a protocol deviation. In Table T5, changed 'Reasons for not receiving airway management' to 'Reasons for not reporting at least one airway management attempt' for clarity.
V2.0	14/04/2018	V3.0	30/07/2018	Clarified in section 5.3, that zero scores for the EQ-5D will be applied for consented patients who are known to have died post discharge. Extended the analysis of the EQ-5D scores to include the option for modelling an ordered categorical outcome, if the log-linear part of the zero-inflated two-part model is a poor fit to the data. Removed the proposed analysis restricted to those who survived to hospital discharge if model fit was poor. An ordered categorical model

				will allow all patients with data to be included. Revised the derivation of 'time to death 0-72 hours' to be consistent with the overall analysis of time to death. Previously different censoring 'rules' applied. Added the derivation of event witnessed by ambulance staff. Revised the derivation of the Utstein comparator indicator; OHCA that are not witnessed are, by definition, in the non-comparator group. This was missed in the previous version of the SAP. Revised derivation of initial ventilation success; if advanced airway management not attempted then ventilation is considered successful (as resuscitation is attempted for all trial patients). Regurgitation and aspiration derivations before advanced airway management and during/after advanced airway management combined into one variable as timing was not specified explicitly in the study protocol. Derivation of ROSC on ED admission added Added estimation of risk differences and risk ratios for analyses of binary outcomes to bring in line with Consort reporting recommendations and to facilitate future meta-analysis. For the time to event analysis, changed clarified when censoring occurred (i.e. according to the derivations in section 5.4)

				Changed 'per-protocol' to 'as-treated' throughout to better reflect what was intended. Added sensitivity analyses for the longitudinal analyses of EQ-5D and mRS, to allow patients who did not consent to active follow-up to be included. The two analyses represent the worse and best-case scenarios. The primary analysis using active consenters plus those who died prior to hospital discharge would likely overestimate the treatment effect. It is anticipated that the best and worse case scenarios will overestimate the treatment effect (whilst allowing more patients to be included in the analysis) and underestimate the treatment effect respectively. Two references were added. Typographical errors were corrected throughout.
V3.0	30/07/2018	V4.0	16/08/2019	Clarified in section 5.1 and section 5.3, that scores of 6 and zero scores for mRS and EQ-5D respectively will be applied for all patients who are known to have died post discharge and that this will be ascertained from the data collected during the course of the trial as well as from HES. Extended the analysis of the EQ-5D scores to include the option for modelling a zero-inflated model with a logistic occurrence part and a beta intensity part if the log-linear part of the zero-inflated two-part model is a poor fit to the data. The zero-inflated two-part model with beta intensity will mean no information is lost as compared to categorising the scores.

				Revised the worst-case scenario sensitivity analysis in section 6.2.6 to add more clarity in terms of what values of scores will be given to patients with missing data based on survival status ascertained from trial data and HES data. Abbreviations managed throughout.

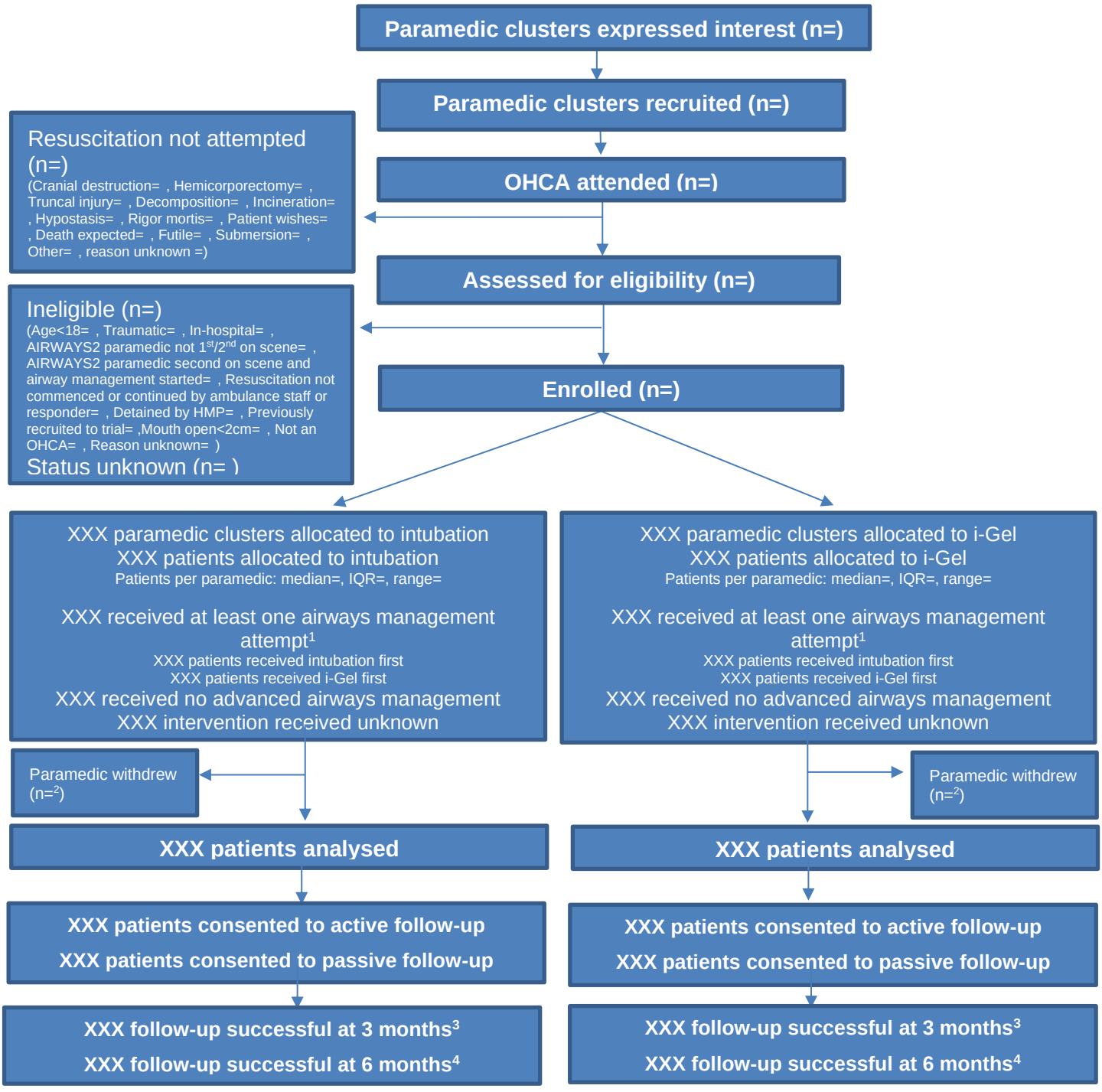
8. REFERENCES

1. Cavrini, G., et al., *Modelling EQ-5D dimensions for the purposes of identifying perceived health impact of lifestyle determinants.* Proceeding of 21st Scientific Plenary Meeting of the EuroQoL Group, 2004. p. 29-44.
2. LLach, X.B., et al., *Determining Correspondence between Scores on the EQ-5D "Thermometer" and a 5-Point Categorical Rating Scale.* Medical Care, 1999. **37**(7): p. 671-677.

APPENDIX A: SKELETON TABLES AND FIGURES

Section	Outputs	
Section 1 Population	**Tables, figures and listings detailing the study population**	
	Figure F1	Flow of participants
	Figure F2	Flow of patients
	Figure F3	Predicted and actual recruitment
	Figures F4 & F5	Predicted and actual recruitment by trust
	Table T1	Initial cardiac arrest details by enrolment status
	Table T2	Protocol deviations
	Table T3	Withdrawals
Section 2 Baseline and intervention data	**Summary tables of demographic information**	
	Table T4	Patient demography and cardiac arrest details
	Table T5	Intervention and post-intervention details
	Figure F6	Interventions received by paramedic allocation
Section 3 Primary and secondary outcome data	**Summary data and group estimates for primary and secondary outcomes**	
	Table T6	Primary outcome
	Table T7	Secondary outcomes
	Table T8	Longitudinal secondary outcomes
	Figure F7	Subgroup analyses
Section 4 Safety data	**Summary tables and listings of all adverse events and serious adverse events**	
	Table T9	Unexpected serious adverse events
	Table T10	Details of unexpected serious adverse events

Figure F1 Flow of paramedics and patients



note:
[1] XXX patients (XXX intubation, XXX i-Gel) received at least one airways management attempt but did not receive i-Gel or intubation. These patients received another SGA.
[2] of the XXX paramedics who withdrew after randomisation, XXX attended an OHCA (XXX Intubation, XXX i-gel) and XXX had not attended an OHCA (XXX intubation, XXX i-gel). Of the former, XXX attended one or more trial patients (XXX Intubation, XXX i-gel). The median number of OHCA attended per withdrawn paramedic is XXX for Intubation (IQR=XXX) and XXX for i-gel (IQR=XXX) The median number of trial patients attended per withdrawn paramedic is XXX for Intubation (IQR=XXX) and XXX for i-gel (IQR=XXX)
[3] XXX patients in the intubation arm and XXX patients in the i-gel arm withdrew prior to 3 months follow-up.
[4] XXX patients in the intubation arm and XXX patients in the i-gel arm withdrew after 3 months and prior to 6 months follow-up.

Figure F2 Flow of patients

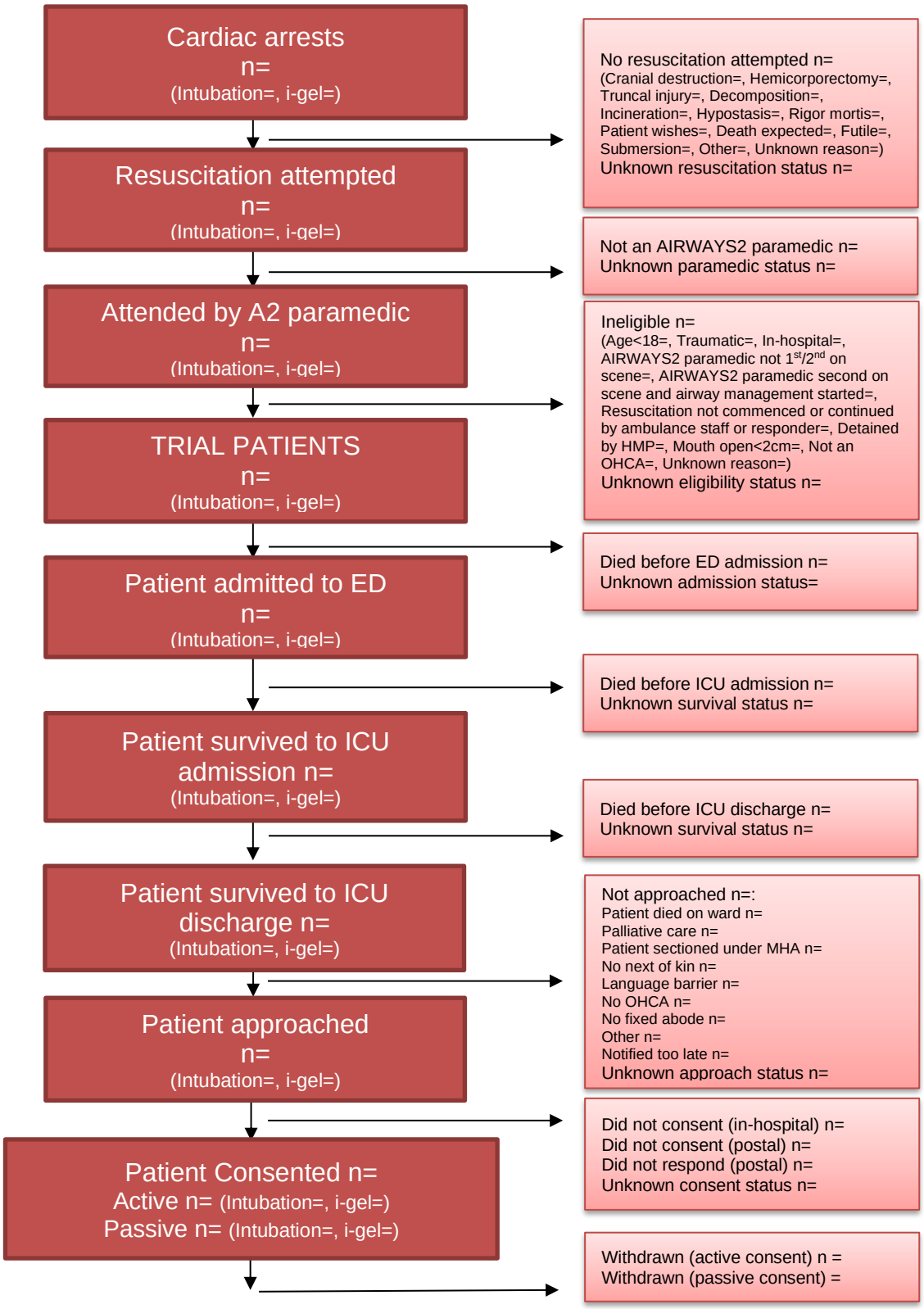


Figure F3 Predicted and actual recruitment

Figure F4 Predicted and actual recruitment by trust (SWAST and YAS)

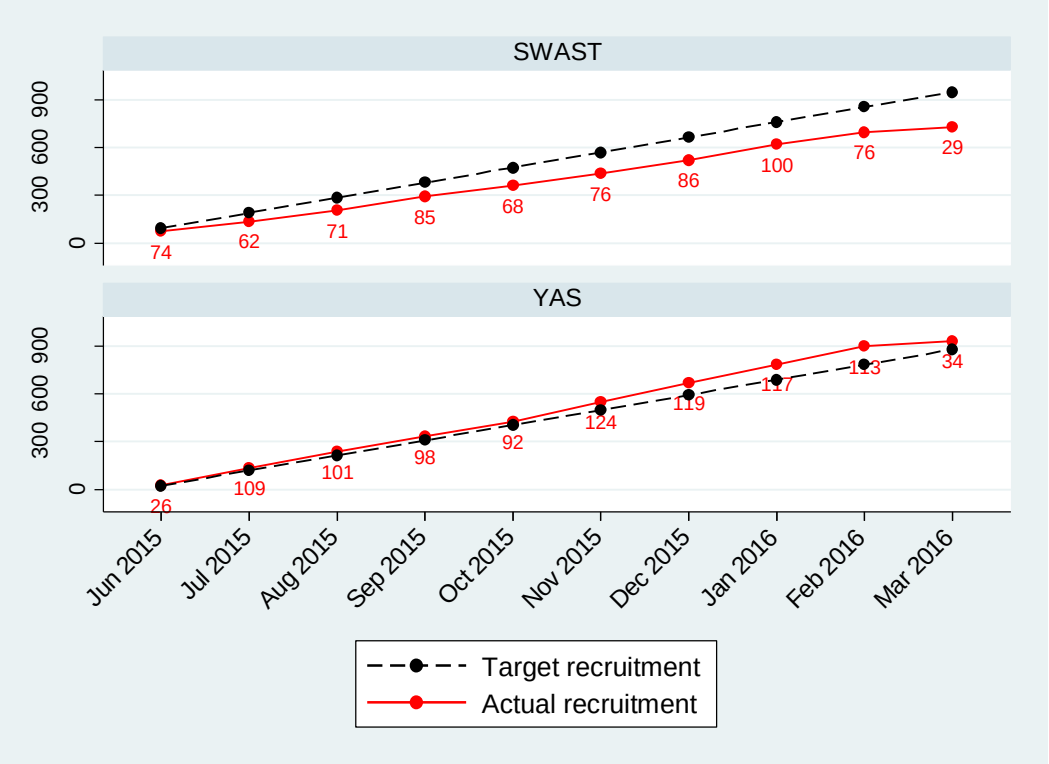


Figure F5 Predicted and actual recruitment by trust (EMAS and EAST)

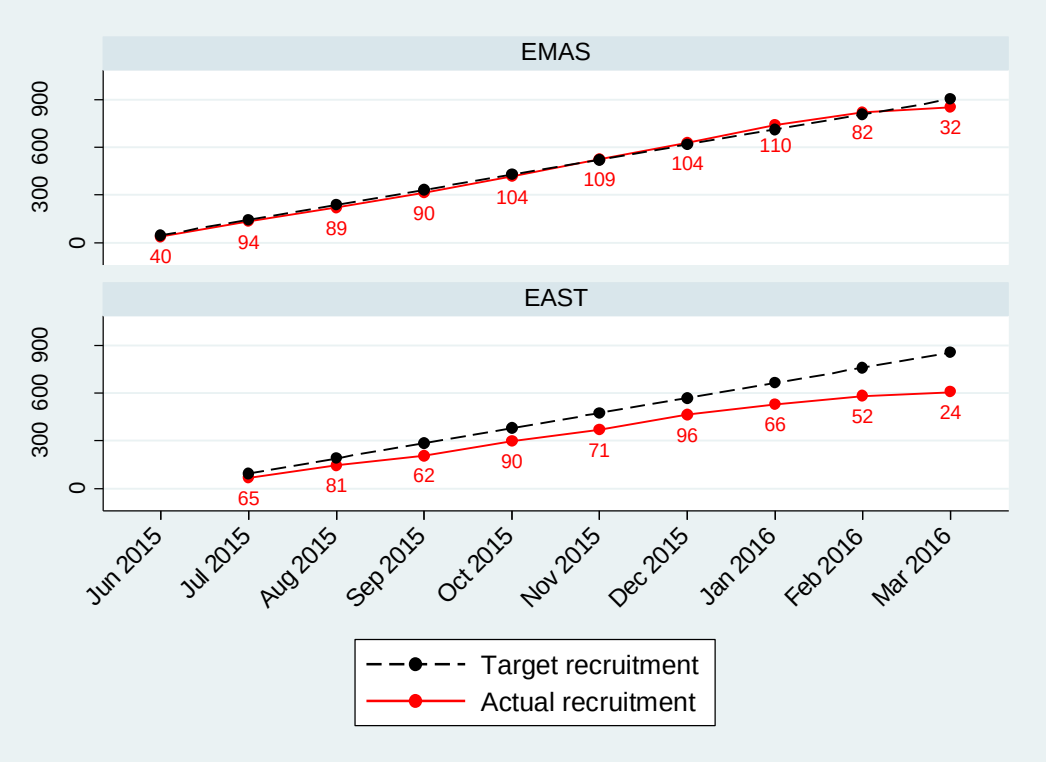


Table T1 Initial cardiac arrest details by enrolment status

	EXCLUDED FROM STUDY					
	Resuscitation attempted but not attended by A2 (n=)		Resuscitation attempted and attended by A2 (n=)		Resuscitation attempted, attended by A2, and eligible. I.e. trial patients (n=)	
	n	%	n	%	n	%
Age (median, IQR)						
Male gender						
999 call to first crew arrival time (mins; median, IQR)						
Presenting rhythm						
Asystole						
VF						
Pulseless VT						
PEA						
Unknown						
Event witnessed						
By EMS						
By bystander						
Bystander CPR						

Note: XXX patients were attended by an A2 paramedic but were not resuscitated.

Table T2 Protocol deviations

	Randomised to intubation (n=XX)		Randomised to i-gel (n=XX)		Overall (n=XX)	
	n	%	n	%	n	%
All trial patients						
Wrong paramedic enrolled patient						
Resulted in randomised allocation crossover						
Enrolling paramedic did not perform any airway management but another paramedic did						
Trial patients with at least one advanced airway management attempt performed						
Enrolling paramedic did not perform allocated intervention on first advanced airway attempt						

Note. All patients grouped by the allocation of the first A2 paramedic on scene.

Table T3 Withdrawals

	Randomised to intubation (n=XX)		Randomised to i-gel (n=XX)		Overall (n=XX)	
	n	%	n	%	n	%
Any withdrawal (paramedics)						
Decision taken by						
Study team						
Paramedic						
Reason for withdrawal						
Reason 1						
Reason 2						
…..						
Any withdrawal (trial patients)						
Timing of withdrawal						
Pre-discharge						
Post-discharge						
Decision taken by						
Health care professional						
Patient						
Reason for withdrawal						
Reason 1						
Reason 2						
…						
…						

Note. This form only applied to patients who consent to active or passive follow-up

Table T4 Patient demography and cardiac arrest details

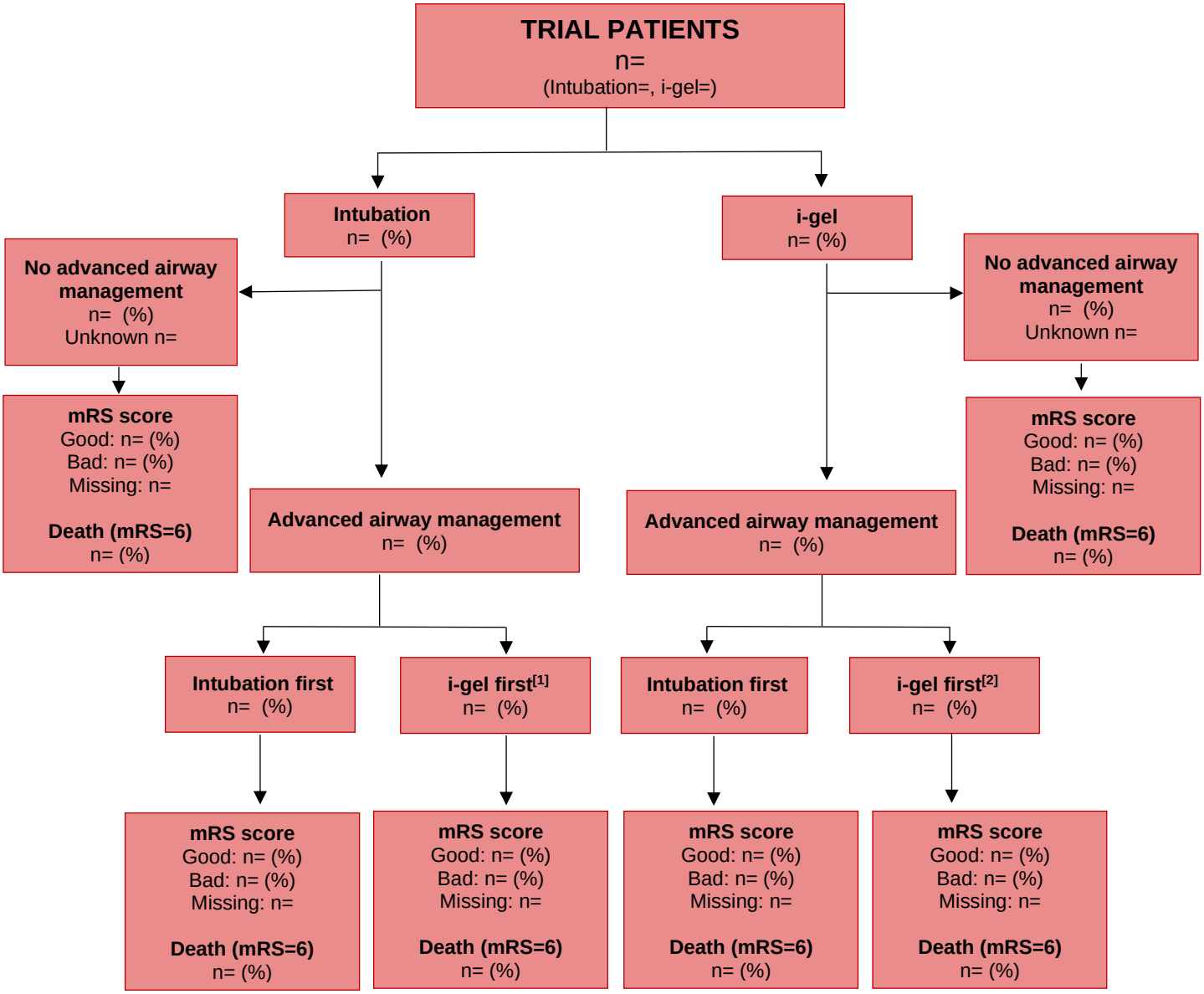
	Randomised to intubation (n=XX)		Randomised to i-gel (n=XX)		Overall (n=XX)	
	n	%	n	%	n	%
DEMOGRAPHY						
Male gender						
Age (median, IQR)						
INITIAL CARDIAC ARREST DETAILS						
999 call to first crew arrival time (mins; median, IQR)						
First crew arrival to A2 arrival time (mins; median, IQR)						
999 call to A2 arrival time (mins; median, IQR)						
Presenting rhythm						
Asystole						
VF						
Pulseless VT						
PEA						
Arrest witnessed						
By EMS						
By bystander						
Bystander/responder CPR before response vehicle arrived						
Bystander/responder defibrillation before response vehicle arrived						
If yes, ROSC achieved						
ON ARRIVAL OF A2 PARAMEDIC						
Patient had ROSC on arrival						
Airway management in progress						
None						
BVM only						
OPA						
NPA						
I-gel						
Intubation						
Other SGA*						
Other*						
Successful ventilations ongoing						

* Details will be provided

Table T5 Intervention details (excluding secondary outcomes)

	Randomised to *intubation* (n=XX)		Randomised to *i-gel* (n=XX)		Overall (n=XX)	
	n	%	n	%	n	%
A2 AIRWAY MANAGEMENT DETAILS						
At least one airway management attempt reported by study paramedic						
Reasons for not reporting at least one airway management attempt						
Resuscitation successful/ceased						
Another paramedic managed airway						
Enrolling paramedic managed airway but cannot remember details						
Patient had a tracheostomy						
Other						
Patient received at least one advanced airway management attempt by an A2 paramedic						
Intubation						
I-gel						
Other SGA						
CO_2 monitoring/ capnography used						
If no, reason:						
Unavailable						
Faulty equipment						
N/A- no advanced airway management						
If yes, type of CO_2 monitoring						
Colour only						
Capnometry (number only)						
Capnography (waveform)						
Mechanical CPR used during resuscitation						
Airway management handed over during pre-clinical care						
If yes, to whom						
Doctor						
Nurse						
Paramedic						

Figure F6 Interventions Received By Paramedic Allocation



[1] XX additional patients received an alternative supraglottic airway device only. Of which XX (%) had a good mRS score, XX (%) had a bad mRS score, XX was missing mRS, and XX (%) had an mRS of 6.

[2] XX additional patients received an alternative supraglottic airway device only. Of which XX (%) had a good mRS score, XX (%) had a bad mRS score, XX was missing mRS, and XX (%) had an mRS of 6.

Table T6 Primary outcome (mRS) and survival status

	Randomised to intubation (n=XX)		Randomised to i-gel (n=XX)			
	n	**%**	**n**	**%**	**Estimate[1] (95% CI)**	**p-value**
mRS (0 to 3; good recovery)					OR[2]	
0 (no symptoms)						
1						
2						
3						
4						
5						
6 (deceased)						
Time from OHCA to time mRS was assessed (median, IQR)						
Survival status:						
Died on scene						
Died prior to ICU admission						
Died prior to ICU discharge						
Died prior to hospital discharge						
Survived to hospital discharge						
Time to death (hours; median, IQR)					HR[3]	
Time to death 0-72h (hours; median, IQR)					HR	
72 hour survival					OR	

[1]OR=Odds ratio, HR=Hazard ratio

[2] ICC

[3] ICC

Table T7 Secondary outcomes and related post-intervention details

	Randomised to intubation (n=XX)		**Randomised to i-gel (n=XX)**			
	median	IQR	median	IQR	**Estimate[1]** (95% CI)	p-value
Compression Fraction					MD/GMR	

	Randomised to intubation (n=XX)		**Randomised to i-gel** (n=XX)			
	n	%	n	%	**Estimate[1]** (95% CI)	p-value
AIRWAY MANAGEMENT DETAILS						
Actual sequence of airway interventions delivered						
Sequence 1						
Sequence 2						
……						
Initial ventilation success (first two attempts) of first advanced airway management						
Intubation						
I-gel						
Other SGA						
Total					OR	
Any ventilation success						
Intubation						
I-gel						
Other SGA						
Total						
Any loss of previously established airway						
Intubation						
I-gel						
Other SGA						
Total					OR	
Regurgitation before initial i-gel/intubation attempt					OR	
If yes, aspiration					OR	
Regurgitation during or after initial i-gel/intubation attempt					OR	
If yes, aspiration					OR	
Any ROSC during advanced A2 airway management					OR	

Any ROSC during any A2 airway management						
Advanced airway management in place when patient first had ROSC						
Intubation						
I-gel						
Other SGA						
Other						
Airway management in place on final attempt by A2 paramedic in those who died on scene						
Intubation						
I-gel						
Other SGA						
Other						
Airway management in place when patient first had ROSC or on final attempt by A2 paramedic in those who died on scene						
Intubation						
I-gel						
Other SGA						
Other						
Total						
Airway management in place on final attempt by A2 paramedic in those who were admitted to ED						
Intubation						
I-gel						
Other SGA						
Other						

	Randomised to intubation (n=XX)		**Randomised to i-gel (n=XX)**			
					Estimate[1]	
	n	%	n	%	(95% CI)	p-value
ED STAY						
Admitted to ED/ hospital						
ROSC on ED/hospital admission					OR	
Survived to ED discharge						
ICU STAY						
Admitted to ICU from ED						
Survived to ICU discharge						

Duration of initial ICU stay in patients who survived to ICU discharge (hours; median, IQR)						
Duration of ICU stay in patients who died in ICU (hours; median, IQR)						
Duration of ICU stay in all patients admitted to ICU from ED (hours; median, IQR)						
HOSPITAL STAY						
Survived to hospital discharge						
Duration of hospital stay in patients who survived to discharge (days; median, IQR)						
Duration of hospital stay in patients who died before discharge (hours; median, IQR)						
Duration of hospital stay in all patients admitted to ED (hours; median, IQR)						

[1]OR=Odds ratio (from logistic or, where marked *, multinomial regression), MD=mean difference, GMR=Geometric mean ratio

Table T8 Longitudinal secondary outcomes

	Randomised to intubation (n=XX)		**Randomised to i-gel (n=XX)**		**Overall (n=XX)**	
	n	**%**	**n**	**%**	**N**	**%**
mRS (0 to 3; good recovery)						
Discharge/30 days						
3 months						
6 months						
Treatment*time interaction						
Overall					OR	

	Randomised to intubation (n=XX)		**Randomised to i-gel (n=XX)**		**Overall (n=XX)**	
	n	**%**	**n**	**%**	**N**	**%**
EQ5D index score (median, IQR)						
Discharge/30 days						
3 months						
6 months						
Treatment*time interaction						
Overall					OR, GMR	
EQ5D visual analogue scale score (median, IQR)						

Discharge/30 days		
3 months		
6 months		
Treatment*time interaction		
Overall		OR, GMR

Figure F7 Subgroup analyses (example for one subgroup analysis: event witnessed by ambulance staff)

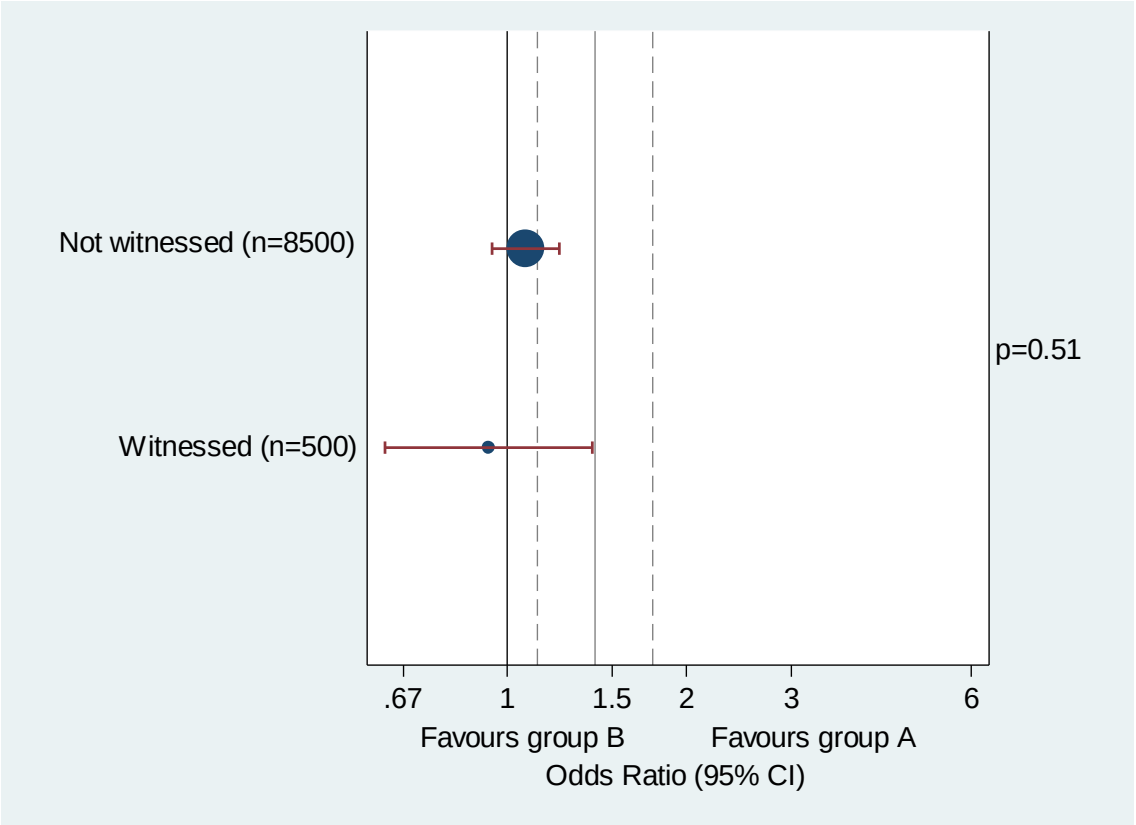


Table T9 Unexpected serious adverse events

		Received Intubation first (n=XX)		Received i-gel first (n=XX)	
		n	%	n	%
Number of patients experiencing one or more SAEs					
Number of events					
Brief description of events					
Timing of events	Pre-surgery				
	Post-surgery but pre-discharge				
	Post-discharge				
Maximum intensity	Mild				
	Moderate				
	Severe				
Reason event classified as SAE	Resulted in death				
	Is/was life threatening				
	Resulted in persistent or significant disability/incapacity				
	Prolonged ongoing hospitalisation/ caused hospitalisation				
	Other				
Relatedness to intervention	Possibly related				
	Probably related				
	Definitely related				

Table T10 Details of unexpected serious adverse events

Study ID=	Intervention randomised to=	Interventions received=	Patient withdrawn from study (and when)=
OHCA date=	Hospital discharge date (if applicable)=	Death date (if applicable)=	Timing of SAE= Post-intervention but pre-discharge/ Post-discharge
Brief description of event=	Location=	Maximum intensity=	Relatedness=
SAE start date/time=	SAE resolution date/time=	Event resulted in death=	Event was life threatening=
Event resulted in persistent/significant disability/incapacity=	Event prolonged ongoing hospitalisation/resulted in hospitalisation=	Other reason for reporting as SAE (with details)=	
Initial report: full details	Initial report: action=	Initial report: other info=	
FUP 1: full details	FUP 1: action=	FUP 1: other info=	
FUP 2: full details	FUP 2: action=	FUP 2: other info=	

APPENDIX B: INDIVIDUAL EQ5D QUESTION DATA

		Randomised to Intubation (n=XX)		Randomised to i-gel (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
MOBILITY							
Discharge/30 days	No problems walking about						
	Slight problems walking about						
	Moderate problems walking about						
	Severe problems walking about						
	Unable to walk about						
3 months	No problems walking about						
	Slight problems walking about						
	Moderate problems walking about						
	Severe problems walking about						
	Unable to walk about						
6 months	No problems walking about						
	Slight problems walking about						
	Moderate problems walking about						
	Severe problems walking about						
	Unable to walk about						
SELF-CARE							
Discharge/30 days	No problems with washing or dressing						
	Slight problems washing or dressing						
	Moderate problems washing or dressing						
	Severe problems washing or dressing						
	Unable to wash or dress						
3 months	No problems with washing or dressing						
	Slight problems washing or dressing						
	Moderate problems washing or dressing						
	Severe problems washing or dressing						
	Unable to wash or dress						

6 months	No problems with washing or dressing Slight problems washing or dressing Moderate problems washing or dressing Severe problems washing or dressing Unable to wash or dress						
USUAL ACTIVITIES							
Discharge/30 days	No problems with usual activities Slight problems with usual activities Moderate problems with usual activities Severe problems with usual activities Unable to perform usual activities						
3 months	No problems with usual activities Slight problems with usual activities Moderate problems with usual activities Severe problems with usual activities Unable to perform usual activities						
6 months	No problems with usual activities Slight problems with usual activities Moderate problems with usual activities Severe problems with usual activities Unable to perform usual activities						
PAIN/DISCOMFORT							
Baseline	No pain or discomfort Slight pain or discomfort Moderate pain or discomfort Severe pain or discomfort Extreme pain or discomfort						
3 months	No pain or discomfort Slight pain or discomfort						

	Moderate pain or discomfort						
	Severe pain or discomfort						
	Extreme pain or discomfort						
6 months	No pain or discomfort						
	Slight pain or discomfort						
	Moderate pain or discomfort						
	Severe pain or discomfort						
	Extreme pain or discomfort						
ANXIETY/DEPRESSION							
Baseline	Not anxious or depressed						
	Slightly anxious or depressed						
	Moderately anxious or depressed						
	Severely anxious or depressed						
	Extremely anxious or depressed						
3 months	Not anxious or depressed						
	Slightly anxious or depressed						
	Moderately anxious or depressed						
	Severely anxious or depressed						
	Extremely anxious or depressed						
6 months	Not anxious or depressed						
	Slightly anxious or depressed						
	Moderately anxious or depressed						
	Severely anxious or depressed						
	Extremely anxious or depressed						