



**A randomised trial of expedited transfer to a cardiac arrest
centre for non-ST elevation out-of-hospital cardiac arrest
(ARREST)**

Trial Protocol Version 3

ISRCTN96585404

Sponsored by King's College London

Funded by the British Heart Foundation

Table of contents

Table of contents	2
1. List of abbreviations	4
1.1. A note on terminology	4
2. Trial summary	5
2.1. Protocol summary	5
2.2. Flow diagram.....	7
3. Introduction	8
3.1. Background	8
3.2. The need for a randomised controlled trial	9
3.3. Pilot study results.....	9
4. Aim	10
5. Endpoints	10
5.1. Primary endpoint	10
5.2. Secondary endpoints	10
6. Power calculations and sample size determination	10
7. Selection of patients	11
7.1. Identification of patients.....	11
7.2. Inclusion criteria.....	11
7.3. Exclusion criteria	11
7.4. Patients entered into observational research	11
8. Ethical considerations	12
8.1. Consent procedures.....	12
8.1.1. Consent waiver prior to enrolment	12
8.1.2. Patient identification in hospital.....	12
8.1.3. Informed Consent	13
8.1.4. Participants who lack capacity	13
8.1.4.1. Personal consultee.....	13
8.1.4.2. Professional consultee	13
8.1.4.3. Assessment of capacity during follow up.....	14
8.1.5. Participants that have died before consent can be obtained.....	14
8.1.5.1. Process for relatives to gather further information	14
8.1.6. Patients that have been discharged before consent can be obtained	15
8.1.7. Withdrawal.....	15
8.2. Declaration of Helsinki and Good Clinical Practice	15
8.3. Ethical committee review	15
8.4. Confidentiality advisory group.....	15
8.5. Trial registration.....	16
9. Randomisation	16
9.1. Randomisation procedure	16
9.2. Access to randomisation site	16
10. Trial treatment	17
10.1. Intervention: Direct to CAC.....	17
10.2. Control: standard of care	17
10.3. Crossover	17
11. Safety reporting	18
11.1. Definition	18
11.2. Expected serious adverse events related to usual clinical care.....	18
11.3. Unexpected serious adverse events	18
11.4. Unexpected non-serious adverse events.....	19
11.5. Reporting unexpected adverse events	19

11.5.1.	Assessment of intensity	19
11.5.2.	Assessment of causality	19
12.	Data collection and follow-up.....	20
12.1.	Trials procedures table	20
12.2.	Data collection	20
12.3.	Trials procedures.....	21
12.3.1.	Pre-hospital care:	21
12.3.2.	In-hospital care:	21
12.3.3.	30 days post-randomisation:	22
12.3.4.	3 months post-randomisation:	22
12.3.5.	6-months post-randomisation:	22
12.3.6.	12-months post-randomisation:	22
13.	Monitoring and auditing	22
13.1.	Monitoring	22
14.	Statistical considerations	23
14.1.	Statistical analysis plan	23
14.2.	Statistical analysis	23
14.3.	Intention to treat	23
14.4.	Planned subgroup analysis.....	23
14.5.	Bias.....	24
14.6.	Potential risks and hazards	24
14.7.	Early termination of trial.....	24
15.	Data handling and record keeping	24
16.	Insurance.....	25
17.	Publications	25
17.1.	Policy.....	25
17.2.	Expected value of results	25
17.3.	Dissemination	25
18.	Trial organisation	26
18.1.	Trial and logistics management	26
18.2.	Trial steering committee.....	26
18.3.	Project management group	26
18.4.	Data and safety monitoring committee.....	27
19.	References.....	28
Appendix A: List of sites and Principal Investigators		33
	London Ambulance Service.....	33
	CAC Sites	33
	Emergency Departments	33
Appendix B: EQ-5D-5L		35

1. List of abbreviations

APP	Advanced paramedic practitioner
ARR	Absolute risk reduction
CAC	Cardiac arrest centre
CARU	Clinical Audit and Research Unit
CPC	Cerebral performance category score
CPR	Cardiopulmonary resuscitation
DSMC	Data and safety monitoring committee
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ECG	Electrocardiogram
eCRF	Electronic case report form
ICA	Immediate coronary angiography
ILCOR	International Liaison Committee on Resuscitation
LAS	London Ambulance Service
LSHTM CTU	London School of Hygiene & Tropical Medicine Clinical Trials Unit
MACCE	Major adverse cardiovascular and cerebrovascular events
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
PI	Principal Investigator
PIS	Patient information sheet
STE	ST-segment elevation

1.1. A note on terminology

The term cardiac arrest centre (CAC) has been used throughout this document in place of heart attack centre (HAC) which was used in the pilot study. The term HAC, while used in London, is not in use in other parts of the United Kingdom or abroad. As such, it was decided to use CAC to reflect the move towards this more commonly accepted term. However, in the patient and consultee information sheets the term HAC has been used to avoid any confusion for patients or consultees.

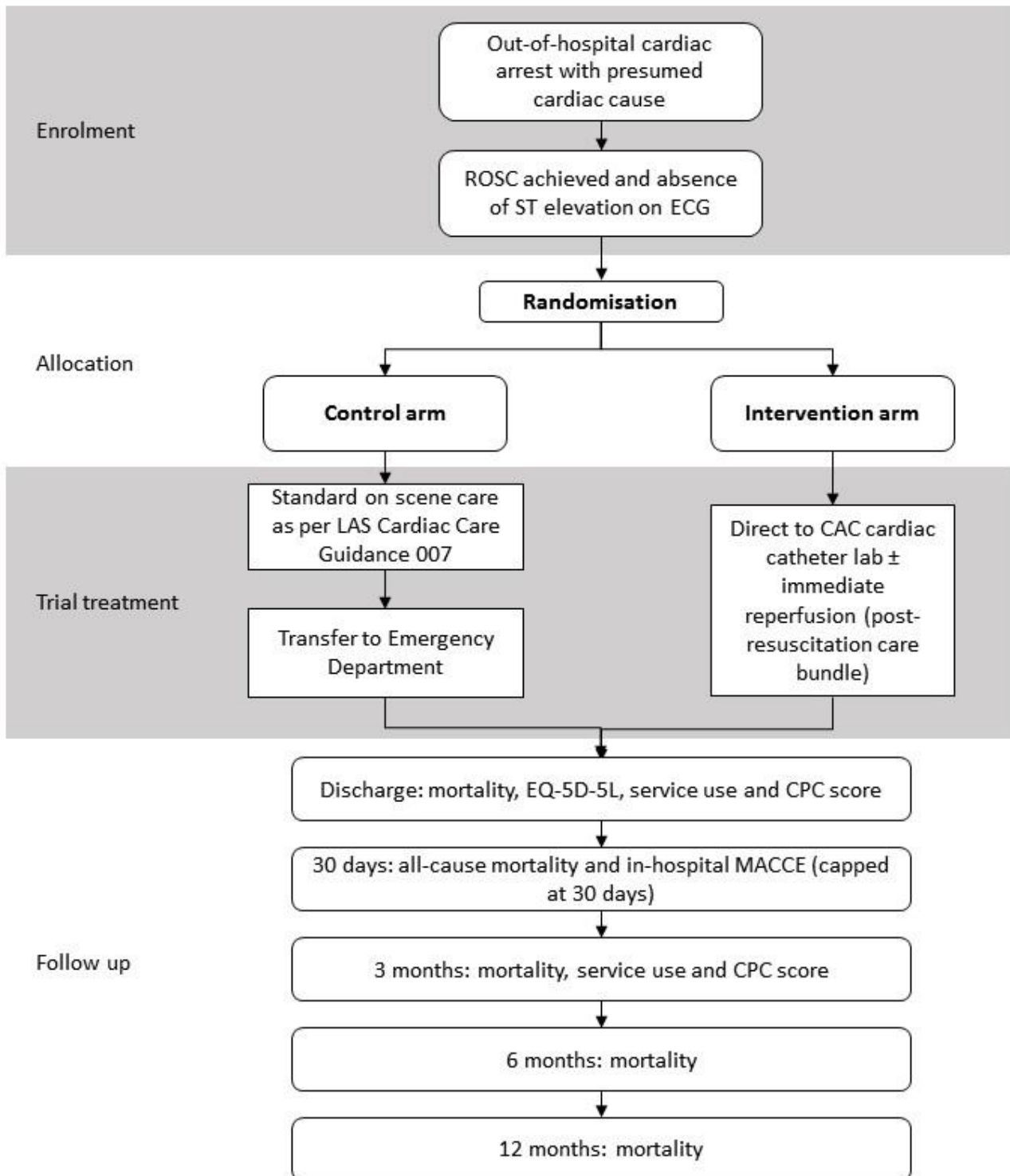
2. Trial summary

2.1. Protocol summary

Abbreviated Title	ARREST
Full Title	A randomised trial of expedited transfer to a cardiac arrest centre for non-ST elevation out-of-hospital cardiac arrest
ISRCTN	ISRCTN96585404 http://www.controlledtrials.com/ISRCTN96585404/ARREST
Brief Description	The aim is to determine the best post-resuscitation care pathway for patients without ST-segment elevation (STE). We propose that changes to emergency management comprising expedited delivery to a cardiac arrest centre (CAC) will reduce mortality in patients without STE compared to the current standard of care.
Trial Type	Randomised controlled interventional trial
Condition	Out-of-hospital cardiac arrest (OHCA)
Intervention	Transfer to a CAC
Trial Arms	1) Treatment arm: Expedited transfer to a CAC 2) Control arm: Current standard of care
Start Date	Pilot trial: November 2014 Full trial: 1 May 2017 for set-up, 1 September 2017 for recruitment
Estimated Enrolment	860 patients: 430 in each trial arm
Estimated Completion	End of recruitment: 31 August 2020 End of follow-up: 31 August 2021 Completion of trial: 30 April 2022

Eligibility Criteria	<p>Inclusion Criteria (all)</p> <ol style="list-style-type: none"> 1. Out-of-hospital cardiac arrest (OHCA) 2. Return of spontaneous circulation (ROSC) 3. Age 18 or over (known or presumed) 4. Absence of non-cardiac cause (for example; trauma, drowning, suicide, drug overdose) <p>Exclusion Criteria (any)</p> <ol style="list-style-type: none"> 1. Criteria for ST-elevation myocardial infarction on 12-Lead electrocardiogram (ECG) 2. Cardiac arrest suffered after care pathway set and patient en route 3. Do Not Attempt Resuscitation (DNAR) order 4. Suspected pregnancy 												
Gender	Both												
Ages	Age 18 or over (known or presumed), no upper age limit												
Healthy Volunteers	No												
Recruitment Status	Open												
UK Sites & Investigators	A list of participating sites and investigators can be found in Appendix A												
Chief Investigator	<p>Prof Simon R Redwood</p> <p>Professor of Interventional Cardiology</p> <p>King's College London/Guy's and St Thomas' NHS Foundation Trust</p> <p>Email: simon.redwood@gstt.nhs.uk</p>												
Co-Principal Investigators	<table> <tr> <td>St Barts' Heart Centre:</td> <td>Dr Miles Dalby</td> </tr> <tr> <td>King's College Hospital:</td> <td>Professor Philip MacCarthy</td> </tr> <tr> <td>Harefield Hospital:</td> <td>Dr Ajay Jain</td> </tr> <tr> <td>St George's Hospital:</td> <td>Dr Zoe Astroulakis</td> </tr> <tr> <td>Royal Free Hospital:</td> <td>Dr Roby Rakhit</td> </tr> <tr> <td>Hammersmith Hospital:</td> <td>Dr Iqbal Malik</td> </tr> </table>	St Barts' Heart Centre:	Dr Miles Dalby	King's College Hospital:	Professor Philip MacCarthy	Harefield Hospital:	Dr Ajay Jain	St George's Hospital:	Dr Zoe Astroulakis	Royal Free Hospital:	Dr Roby Rakhit	Hammersmith Hospital:	Dr Iqbal Malik
St Barts' Heart Centre:	Dr Miles Dalby												
King's College Hospital:	Professor Philip MacCarthy												
Harefield Hospital:	Dr Ajay Jain												
St George's Hospital:	Dr Zoe Astroulakis												
Royal Free Hospital:	Dr Roby Rakhit												
Hammersmith Hospital:	Dr Iqbal Malik												

2.2. Flow diagram



3. Introduction

3.1. Background

Out-of-hospital cardiac arrest (OHCA) is a global public health issue. There are 60,000 cardiac arrests per year in the UK, of which resuscitation is attempted in just under half.^{1,2}

Resuscitation attempts are successful in up to 30%. However, more than two thirds of patients who survive to hospital admission die before discharge. There is wide variation in both regional and inter-hospital survival rates from OHCA; this disparity is also present across London.²⁻⁹ This variation has been shown to be attributable to hospital infrastructure, resources and personnel rather than patient characteristics.¹⁰ Overall survival therefore remains poor, at 7%.¹¹

OHCA places a substantial burden on the NHS. Healthcare costs (including emergency response, hospitalisation and long-term care of survivors) amount to more than £50,000/patient.¹²⁻¹⁴ Regionalisation of care into specialist centres has played a vital role in the management of time-critical illnesses through concentration of services and greater provider experience.¹⁵⁻²⁰ These organised systems of care have the potential to improve survival post-cardiac arrest, with an associated reduction in the economic burden.^{12, 13, 21}

The International Liaison Committee on Resuscitation (ILCOR) suggest transport of the post-arrest patient to a cardiac arrest centre (CAC) with 24/7 access to interventional cardiology facilities to manage the ensuing cardiovascular dysfunction and diagnose and treat the underlying cause to increase the probability of survival.²²⁻²⁵ The coordination of this is complex and close interaction is necessary pre-hospital between centres and ambulance services and internally between the Emergency Department, Cardiologists, and Critical Care.

It is well known that the majority of OHCA are secondary to an acute cardiac ischaemic event. Coronary artery disease is responsible for more than 70% of OHCA of presumed cardiac cause, with acute occlusion demonstrated in 50% of consecutive patients taken for immediate coronary angiography (ICA).²⁶ Early cardiopulmonary resuscitation (CPR) and defibrillation, with ICA and percutaneous coronary intervention (PCI) in a CAC, prevents re-arrest, preserves myocardial function and has been shown to improve post-arrest outcomes in ST-segment elevation (STE).^{8, 27-32}

It is difficult to conclude which of the components of post-arrest care is essential, given the observational nature of studies.³ Targeted temperature management has been shown to improve neurological survival.^{33, 34} There is also expert consensus that early reperfusion therapy in STE reduces mortality (Class I recommendation).³⁵⁻³⁷

The management of patients without STE however is controversial, with a delayed approach to intervention. Despite recently published data suggesting PCI in non-STE resulted in a two-fold increase in favourable outcome²⁷, randomised data are lacking. Emergent reperfusion therapies come with a weak recommendation from ILCOR, and a Class IIa recommendation by the American Heart Association (AHA) and European Society of Cardiology (ESC), if there is a high suspicion of ongoing infarction.^{36, 38}

The European Association of Percutaneous Cardiovascular Interventions (EAPCI) recommends a prior rule-out of non-cardiac cause in the emergency department followed by coronary angiography within 2 hours.²³ It remains unclear if time-critical, definitive hospital based management of the post-arrest patient without STE in a specialist centre improves outcomes, and there has been variable uptake of this strategy both pre-hospital and amongst the interventional cardiology community.

3.2. The need for a randomised controlled trial

There is an urgent need for a randomised controlled trial examining the benefits of early delivery of post-cardiac arrest care in specialist centres, specifically in the absence of STE. Post-arrest care is time-critical, requires a multi-disciplinary approach and may be more optimally delivered in centres with greater provider experience. ILCOR and the EAPCI state that randomised trials are essential in this population to determine if timely delivery by the ambulance services to a CAC with organised post-cardiac arrest care including immediate access to reperfusion therapy improves survival.^{3, 23} There are no randomised trials and only indirect evidence that CAC and systems of care may be effective and only two observational studies examining the role of immediate ICA±PCI in the absence of STE. This is an important and topical question as there is a drive to regionalise care for all patients into CACs.

3.3. Pilot study results

The pilot was a feasibility study (that also assessed safety and efficacy outcomes) undertaken by London Ambulance Service (LAS), St. Thomas' Hospital CAC, the London School of Hygiene and Tropical Medicine Clinical Trials Unit (LSHTM CTU) and the neighbouring district general hospitals within St Thomas' CAC catchment area.

40 patients were randomised, 10 patients were recruited between November 2014 to March 2015 and 30 patients between August 2015 to February 2016, with an increase in recruitment rate during the study period. On comparison with independently collected clinical OHCA audit data, 63% of all eligible patients were recruited over these time periods.

Feasibility data have been presented and published.³⁹ These data demonstrated no clear safety concerns and recruitment rate indicated the feasibility of proceeding to a larger scale trial.

4. Aim

The aim is to determine the best post-resuscitation care pathway for patients without STE. We propose that changes to emergency management comprising expedited delivery to a CAC with organised post-cardiac arrest care including immediate access to reperfusion therapy will reduce mortality in patients without STE compared to the current standard of care, which comprises protracted pre-hospital management of the patient without definitive care plan and delivery to geographically closest hospital.

5. Endpoints

5.1. Primary endpoint

All-cause mortality at 30 days.

5.2. Secondary endpoints

The impact on the following outcomes will be assessed.

- Neurological status at 3 months
- All-cause mortality at 3, 6 and 12 months
- The composite of in-hospital major adverse cardiovascular and cerebrovascular events (MACCE) capped at 30 days
- EQ-5D-5L at discharge

6. Power calculations and sample size determination

Mortality at 30 days in the control arm is expected to be approximately 60% for the type of patients recruited into ARREST. This figure is based on Pan London OHCA data (87% mortality with ROSC at any time post cardiac arrest and 73% mortality with ROSC maintained to hospital), registry data and the pilot study.

Observational studies on implementation of treatment bundles have shown absolute risk reductions (ARR) of near 30% compared to the baseline comparator and the Parisian group have shown ARR of 16% following PCI in non-STE.^{3, 40, 41} If half of the population in question will have a treatable lesion and the combined treatment effect of this within a treatment bundle is examined, a 10% ARR will be practical from 60% to 50% mortality.

A trial of 860 patients (430 in each arm) provides 80% to detect an absolute reduction of 10% (ie 60% to 50%) with up to 10% losses to follow-up and a 5% significance level. If the mortality is higher than 60% then the power will increase to detect a 10% absolute reduction in mortality.

7. Selection of patients

7.1. Identification of patients

Patients with confirmed cardiac arrest will be assessed for eligibility by the attending LAS paramedic. Due to the emergency context of the research, identification cannot be performed in advance. Patients who re-arrest after they have been randomised into the trial will not be excluded and will be conveyed to an ED or CAC as indicated by their treatment allocation. If the patient re-arrests on scene and there is recognition of life extinct by the attending paramedic after randomisation, the patient will not be transferred to an ED or CAC. The patient will remain in the trial and patient data will be collected as discussed in section 9.1.5.

7.2. Inclusion criteria

Patients must meet *all* of the following criteria:

1. Out-of-hospital cardiac arrest (OHCA)
2. Return of spontaneous circulation (ROSC)
3. Age 18 or over (known or presumed)
4. Absence of non-cardiac cause (for example; trauma, drowning, suicide, drug overdose)

7.3. Exclusion criteria

Patients will be excluded if they meet *any* of the following criteria:

1. Criteria for ST-elevation myocardial infarction on 12-Lead electrocardiogram (ECG)
2. Do Not Attempt Resuscitation (DNAR) Order
3. Cardiac arrest suffered after care pathway set and patient en route
4. Suspected pregnancy

7.4. Patients entered into observational research

Patients may be entered into registries or observational studies while also participating in ARREST.

8. Ethical considerations

8.1. Consent procedures

There are a number of important issues in the consent procedure that have been considered. These include the enrolment of patients while they are in cardiac arrest, the handling of data and follow-up for patients who are unable to give their consent due to lack of capacity, and the handling of data from patients who have died. These considerations are discussed below and a flowchart detailing the consent procedure is provided in Appendix B.

8.1.1. Consent waiver prior to enrolment

Due to the emergency nature of the trial and the immediacy of the intervention, the need for prior informed consent has been waived.⁴²

8.1.2. Patient identification in hospital

A research paramedic will contact the named local collaborator/s at the destination hospital (either the CAC or emergency department depending on randomised allocation). The named local collaborator/s will be a member of the direct care team at the hospital delegated by the local PI.

Once identified the patient or consultee may then either;

- a) Be approached for consent or to make a declaration on the patient's behalf by a member of the direct care team (see 9.1.3)
 - b) Be approached for consent or to make a declaration on the patient's behalf by a research paramedic (see 9.1.3)
- OR
- c) Asked if they can be contacted by a local researcher, a researcher allocated from the local research network or a research passport holder. If the patient or consultee agree to this the appropriate person should be contacted and they will be responsible for gathering consent or a consultee declaration.

A research paramedic, or a member of the direct care team, must make the first approach to the patient, their friends or family, or a professional consultee.

The patient or family member's wishes regarding further contact will be adhered to without affecting the patient's standard of care in any way.

8.1.3. Informed Consent

If the patient regains capacity following the cardiac arrest, informed consent should be gathered once the initial emergency has passed.^{43,44} The earliest practicable time is anticipated to be once the patient is discharged from ICU (if this was clinically indicated) and is on a hospital ward.

Consent will be obtained by research paramedics, or by a trained member of staff delegated to do so by the site PI. The patient will be given the patient information sheet (PIS) and allowed sufficient time to consider it fully and have any questions they may have addressed.

If patients wish not to be followed up, consent will be sought to gather data from medical records. Non-identifiable data up until that point will be retained unless the patient explicitly declines permission.

8.1.4. Participants who lack capacity

A consultee should be approached if the patient is alive but does not regain capacity. If the patient has died a consultee **should not** be approached for written consent. Please see section 9.1.5.

8.1.4.1. Personal consultee

As soon as practicable, and at a time which will cause the least distress to the patient and relatives, a friend, partner or relative of the patient should be informed that the patient has been entered into the trial. The decision to approach a friend, relative or partner is at the discretion of a research paramedic in consultation with the direct care team. If it is felt that this would cause undue distress a professional consultee may be contacted instead (see 9.1.3.3).

If appropriate the friend, relative or partner's advice should be taken on whether they think the patient would wish to be part of the trial, particularly if the patient had expressed any prior wishes or advanced decisions. A personal consultee declaration form should be completed, this will be obtained by a registered healthcare professional delegated to do so by the site PI.

8.1.4.2. Professional consultee

A professional consultee may be used in cases where either a family member or friend is unwilling or unable to act as a personal consultee, or the family or friends are not present or available.

This may either be;

- a) A doctor or healthcare provider responsible for the medical treatment provided to the patient, as long as that person is independent of the trial.

OR

- b) A person independent of the trial nominated by the doctor or healthcare provider primarily responsible.

Their advice should be taken on whether they think the patient would wish to be part of the trial. A professional consultee declaration form should be completed, this will be obtained by a registered healthcare professional delegated to do so by the site PI.

Regardless of whether a professional consultee declaration has been collected, if a personal consultee becomes available and it is appropriate to approach them then their advice should be sought on the continued involvement of the patient.

If the patient regains capacity before the one year follow-up visit, the patient should be approached to give informed consent regardless of whether a consultee declaration form has been completed.

8.1.4.3. Assessment of capacity during follow up

At the follow-up time points the personal or professional consultee will be contacted. They will be asked if the researcher may speak to the patient.

- If on assessment it is found that the patient still lacks capacity the consultee will be asked to respond on behalf of the patient.
- If the patient is found to have capacity then the patient information will be provided about the trial and consent sought.

8.1.5. Participants that have died before consent can be obtained

If a patient does not regain capacity and dies before it is possible to gather written consent, mortality data available to LAS will be collected, without patient identifiable data, on the trial database.

8.1.5.1. Process for relatives to gather further information

It is not appropriate to actively inform relatives that the deceased patient has been entered into the trial due to the risk that the receipt of that information may cause additional stress at a traumatic time. There are also practical barriers to providing the information, the sudden and unexpected nature of cardiac arrest will mean relatives may not be present or identifiable.

A website containing details of the trial will be set up with details of the trial and a contact number, email address and postal address to contact for more information. Relatives can therefore make a choice themselves about whether they wish to seek further information, and at a time that suits them. This method has been used successfully on the PARAMEDIC-2 trial.

8.1.6. Patients that have been discharged before consent can be obtained

If the patient is discharged from hospital before contact can be established the research paramedics will first verify that the patient is alive.

- If the patient is found to have died then mortality data will be gathered by LAS (see 9.1.5.)
- If the patient is alive an invitation letter and information sheet will be posted to their discharge address as soon as possible.

If there is no response after two weeks the research paramedic will try to contact the patient by telephone (if a contact number is known) or by a second letter. The patient will be given the option of replying by phone, email or by returning a reply slip. The patient will either then be contacted to complete a consent form or their withdrawal will be recorded.

Non-identifiable data will be collected using mortality tracking, review of patient notes, and data linkage where appropriate on those patients for which no reply has been received.

8.1.7. Withdrawal

A patient may decide to withdraw from the trial at any time without prejudice to their future care.

If the patient has previously consented, NHS records will continue to be used to gather endpoint data unless the patient explicitly denies permission for us to do this.

8.2. Declaration of Helsinki and Good Clinical Practice

The trial will conform to the spirit and the letter of the declaration of Helsinki, and in accordance with the Good Clinical Practice guidelines.

8.3. Ethical committee review

The trial was granted ethical approval (Pan-London) by the National Research Ethics Committee (REC 13/LO/1508) in January 2014.

8.4. Confidentiality advisory group

Due to the nature of the trial, there are three possible instances where patient identifiers in the absence of consent will need to be accessed by researchers.

1. During the identification process LAS research paramedics will access LAS records in order to identify patients.
2. Patients who are entered into the trial but do not regain the capacity to consent and die shortly after enrollment before a consultee declaration can be gathered. In these cases it is key that the trial is able to retain the non-identifiable data for analysis.

3. Patients for whom there is no consent or consultee declaration, have been transferred to another hospital and have not replied to multiple contact attempts from the research team. In these cases it is key that the trial is able to track mortality data on these patients for the primary endpoint and retain non-identifiable data for analysis.

Permission **will be sought from (WHEN APPROVED UPDATE TO: has been granted by)** CAG to allow the use of identifiable data as outlined above. The CAG reference number is 17/CAG/0151

8.5. Trial registration

The trial was prospectively registered with the International Standard Randomised Controlled Trials Registry (ISRCTN98596585404).

9. Randomisation

9.1. Randomisation procedure

Designated LAS staff at the Advanced Paramedic Practitioner (APP) dispatch desk will randomise patients into the intervention arm or control arm using the following procedure:

- Paramedics attending a suspected OHCA will assess the patient for eligibility. Once eligibility is confirmed, the on-site paramedic will ask the APP desk to randomise the patient into the trial.
- The on-site paramedics will call the APP dispatch desk to provide the patient details required to complete randomisation.
- The APP desk staff will access the randomisation site, enter the required details, and generate a study ID and treatment allocation. Patients will be randomised either to an expedited transfer to a CAC (see section 11.1) or to receive standard of care (see section 11.2).
- The APP desk will inform the on-site paramedic which group the patient has been randomised to, and the on-site paramedic will proceed as appropriate.
- The APP desk will provide the necessary information to the Clinical Audit and Research Unit (CARU) at LAS for them to track the patient report form (PRF) to gain clinical data.

9.2. Access to randomisation site

Access to the randomisation site sealedenvelope.com will be strictly controlled and available only to delegated staff of the APP desk at LAS that have received appropriate training. Delegation and training logs will be recorded both at LAS and at the LSHTM CTU. Each staff member will have a unique account

for accessing the randomisation site, and will not share these details of their account with other staff members.

If a staff member is unable to access their account, they should contact the LSHTM CTU to request an account reset. APP desk staff will log in to their accounts at the beginning of each shift and remain logged in for the duration of the shift. Each session will time out after 12 hours. The daily login to the account will mitigate the risk of staff forgetting their login details and losing access to the randomisation service.

10. Trial treatment

10.1. Intervention: Direct to CAC

The intervention arm consists of activation of the pre-hospital triaging system currently in place for post-arrest STE patients. This involves pre-alert of the CAC and strategic delivery of the patient to the catheter laboratory (24 hours a day, 7 days a week). Patients will receive definitive post-resuscitation care: intubation and ventilation, where necessary, targeted temperature management, and goal-directed therapies including evaluation and identification of underlying cause of arrest with access to immediate reperfusion if necessary.^{24, 45} Prognostication will occur no earlier than 72 hours post-cardiac arrest to prevent premature withdrawal of life-sustaining treatment.⁴⁶ Transfer times estimated from the 40-patient pilot are anticipated to be 100 minutes (median; IQR 75 to 113) from time of arrest to the designated centre.

10.2. Control: standard of care

The control arm comprises the current standard of pre-hospital advanced life support (ALS) care management for patients with ROSC following cardiac arrest of suspected cardiac aetiology. The patient is conveyed to the geographically closest emergency department. Management thereafter will be as per standard hospital protocols however as in the intervention arm, prognostication is to be delayed in trial patients until at least 72 hours post arrest.⁴⁶

10.3. Crossover

This likelihood of crossover is anticipated to be low in patients with ROSC in the absence of STE on the ECG. If a clinical decision is made either by the paramedic staff or the in-hospital care team that the patient in the standard of care arm should receive urgent coronary angiography, this will not be considered crossover.

Extensive paramedic training will be provided to prevent inappropriate crossover, however if this does happen the patient will remain in the trial (in the arm they were randomly assigned to) as part of the intention to treat (ITT) analysis.

11. Safety reporting

11.1. Definition

Events that are collected on the electronic case report form (eCRF) or are part of the usual complications post cardiac arrest do not need to be reported for this trial. Unexpected adverse events should however be reported to the ARREST CTU.

Safety reporting for each patient should commence from time of randomisation to completion of follow up at one year after randomisation.

11.2. Expected serious adverse events related to usual clinical care

These events are recognised complications of cardiac arrest. They will be recorded on the eCRF but do not need to be reported separately on an SAE form:

1. Death
2. Myocardial Infarction
3. Stroke
4. Neurological complications
5. Multi-organ failure

The following are considered expected adverse events for cardiac arrest patients undergoing routine clinical care and as such do not need to be reported:

1. Vascular complications
2. Emergency surgery

11.3. Unexpected serious adverse events

Any untoward medical occurrence/effect that:

1. Results in death
2. Is life-threatening*
3. Requires hospitalisation or prolongation of existing inpatient's hospitalisation
4. Results in persistent or significant disability or incapacity

**Life-threatening* in the definition of a serious adverse event refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

SAEs should be reported to the CTU within 7 days. The report should include an assessment of causality by the Principal Investigator (PI) at each site. The Chief Investigator (CI) will be responsible for the prompt notification of findings that could adversely affect the health of patients or impact on the conduct of the trial. Notification of confirmed unexpected and related SAEs will be to the sponsor, the Research Ethics Committee (REC) and the Data and Safety Monitoring Committee (DSMC).

11.4. Unexpected non-serious adverse events

The PI or research nurse should evaluate unexpected non-serious adverse events. This should include an assessment of causality and intensity and reports made within 14 days. The CTU will keep detailed records of all unexpected adverse events reported. The CI will review reports to consider intensity, causality and expectedness. As appropriate, these will be reported to the sponsor, the DSMC and the REC.

11.5. Reporting unexpected adverse events

Investigators will make their reports of all unexpected adverse events, whether serious or not, to the ARREST CTU by email to arrest@LSHTM.ac.uk or by secure fax to 020 7927 2189.

11.5.1. Assessment of intensity

Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning; the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

11.5.2. Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the adverse event and the treatment

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the adverse event and the treatment

Unlikely: A causal relationship is improbable and another documented cause of the adverse event is most plausible.

Unrelated: A causal relationship can definitely be excluded and another documented cause of the adverse event is most plausible.

12. Data collection and follow-up

12.1. Trials procedures table

	Pre-hospital	On arrival to hospital	In hospital	30 days	3 months	6 months	12 months
Review of eligibility criteria	X						
ROSC assessment	X	X					
Randomisation	X						
Transfer to CAC or hospital	X						
PIS & Informed consent / Personal Consultee / Professional Consultee			X				
Neurological status			X		X		
Mortality status		X	X	X	X	X	X
EQ-5D-5L				X			
Service use questionnaire				X	X		
SAE / NSAEs	X	X	X	X	X		

12.2. Data collection

The research paramedics at LAS will collect data for pre-hospital care from the patient report form (PRF) until the patient is consented. If the patient dies before consent is obtained research paramedics will collect mortality data. Delegated research nurses will collect data for in-hospital care and the 30-day, 3-month, 6-month and 12-month follow-up time points.

12.3. Trials procedures

12.3.1. Pre-hospital care:

- Group assignment (Intervention or Control)
- Time of arrest
- Location of arrest
- Arrival time of first responder
- CPR start time
- Ambulance arrival time
- Time of first LAS defibrillation
 - Total number of shocks
- Time of first public access defibrillation (PAD)
 - Total number of shocks
- Cardiac arrest drugs administered
- ROSC pre-hospital
- 12 Lead ECG
- Type of rhythm (initial)
- Use of mechanical CPR
- Survival to hospital
- Time LAS left scene
- Name of first hospital
- Arrival time at first hospital
- Confirmation that treatment allocation was carried out as randomised
- AVPU scale on arrival
- Cerebral performance category (CPC) score on arrival
- Glasgow coma score (GCS) on arrival
- Advanced airway management (i-gel or endotracheal tube)
- Ventilated

12.3.2. In-hospital care:

- Angiogram completed
 - Date and time
 - Extent of coronary artery disease (CAD)
- Revascularisation
 - PCI or CABG
 - If PCI, which artery
 - Call to balloon
 - Door to balloon
 - PCI success
- Complications
 - Troponin elevation
 - Myocardial infarction
 - Stroke
 - Repeat revascularisation
 - Bleeding
 - Mechanical CPR related complications
 - Need for dialysis/haemofiltration
 - Creatinine collected
 - eGFR collected

- Sepsis
- Vascular complications
- Other complications
- LV function on echo
- Chest x-ray findings
- Implantable cardioverter defibrillator inserted
- Service use
- Patient mortality
- CPC at discharge
- Date of discharge
- Quality of life (EQ-5D-5L) at discharge (capped at 30 days)

12.3.3. 30 days post-randomisation:

- Patient mortality
- 30 day hospitalisation status

12.3.4. 3 months post-randomisation:

- Patient mortality
- CPC score by telephone
- Service use questionnaire by telephone

12.3.5. 6-months post-randomisation:

- Patient mortality

12.3.6. 12-months post-randomisation:

- Patient mortality

13. Monitoring and auditing

13.1. Monitoring

The conduct of the trial will be supervised by trained staff from the LSHTM CTU. The trial will be monitored on a regular basis using central statistical monitoring. On site monitoring will take place if considered necessary by the LSHTM CTU or if requested by the trial site.

Local investigators shall ensure that all trial data are available for trial related monitoring, audits and research ethics committee review.

The CTU will periodically monitor consent forms and consultee declarations obtained by LAS research paramedics to ensure that the consent procedure is being correctly followed.

14. Statistical considerations

14.1. Statistical analysis plan

A detailed statistical analysis plan will be produced prior to any patient being randomised due to the radical difference between the interventions in the two trial arms, which therefore cannot be blinded.

14.2. Statistical analysis

The primary analysis will be a comparison of all-cause mortality 30 days after randomisation between the two arms. A risk ratio together with a 95% confidence interval and p-value will be calculated together with the risk difference in all-cause mortality at 30 days. Similarly, these analyses will be undertaken for all-cause mortality at 3, 6 and 12 months. Kaplan-Meier curves will be produced to show all-cause mortality to 30 days and to 12 months. Survival techniques will be used to compare in hospital MACCE given the differing lengths of time patients might be in-hospital. Hazard ratios will be presented from Cox proportional hazards modelling. Neurological status will also be compared at 3 months using the CPC score (an ordinal score from 1 (normal neurological status) to 5 (dead), according to the most commonly used post-resuscitation outcome measurement for this purpose.⁴⁷ Ordered logistic regression will be used to compare the two treatments and a trend test computed. Although the subjectivity of this scoring system and its agreement with other markers of neurological status has been questioned, it remains the most commonly used and standard outcome measure of neurological status in post-cardiac arrest survivors.⁴⁸⁻⁵⁰

14.3. Intention to treat

Intention to treat (ITT) analysis will be performed as the primary statistical method; this includes all randomised patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, treatment they actually received, and subsequent withdrawal from treatment or deviation from the protocol.⁵¹

14.4. Planned subgroup analysis

A limited number of subgroup analyses on the primary endpoint will be undertaken using logistic regression including an interaction between the characteristic and the intervention with effect estimates and confidence intervals produced. In addition, a subgroup analysis will be undertaken by developing a model using logistic regression and categorizing patients according to their underlying risk of dying within 30 days. This simultaneously accounts for the multiple risk factors a patient may have at baseline and will assess whether intervention is more effective at higher underlying risk again using interactions tests.

14.5. Bias

The major sources of bias in this trial are potentially a differential loss to follow up in the two arms and unblinding of patients and clinicians due to the radically different pathways.

It is not anticipated bias will affect the primary outcome of all-cause mortality as this is an objective measure.

14.6. Potential risks and hazards

A potential risk is the inclusion of patients with non-cardiac causes of arrest. This will be mitigated by exclusion of non-obvious cardiac cause during eligibility assessment. 30-day all-cause mortality and in-hospital MACCE will enable identification of such risk with DSMC interim analysis.

14.7. Early termination of trial

A fully independent DSMC will be established to monitor the safety of patients in the trial and a detailed Data Monitoring Charter will be developed. The sample size will not be adjusted to account for interim analyses; however stringent guidelines will be used for the stopping criteria for a benefit of the intervention.⁵²

The trial will be terminated if there is substantial or sufficient evidence of a benefit of the intervention or an increased mortality risk compared to control. The DSMC will also monitor recruitment and other trial progress.

If the required number of patients is completed in advance of estimated recruitment time then the trial may be completed ahead of schedule depending on the event rates observed. Alternatively, if resources are available recruitment may continue in order to maximise the power of the trial.

15. Data handling and record keeping

Data will be entered onto an online database and stored securely on Rackspace servers; <http://www.rackspace.co.uk> and managed by Sealed Envelope. Data will be kept for 15 years following completion of the trial. The data controller for the trial is the Chief Investigator (St Thomas' Hospital is the data controller's organisation) and the data processor is the LSHTM CTU.

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data protection act and LSHTM SOPs.

16. Insurance

All centres will be covered by NHS indemnity for negligent harm providing researchers hold a contract of employment with the NHS, including honorary contracts held by academic staff. Medical co-investigators will also be covered by their own medical defence insurance for non-negligent harm.

King's College London provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions).

17. Publications

17.1. Policy

Publications will follow the CONSORT guidelines. Authorship will follow international guidelines.

17.2. Expected value of results

There are no randomised control trial (RCT) data demonstrating that time critical delivery to a CAC for definitive care improves survival, and the management of patients without STE is controversial. Survival following OHCA remains extremely poor in this cohort at huge cost to the NHS. There is an urgent need for RCT data examining the benefits of urgent delivery of post-cardiac arrest care in specialist centres, specifically in the absence of STE. Post-arrest care is time-critical, requires a multidisciplinary approach and may be more optimally delivered in centres with greater provider experience.

This trial would demonstrate if regionalisation of post-arrest care to specialist centres reduces mortality in the non-STE cohort, thus dramatically reshaping emergency care provision. Either supporting or refuting the current drive, in the lack of randomised data, to immediately transport all post-arrest patients with non-obvious cardiac cause to a CAC.

17.3. Dissemination

It is our intention to disseminate the results of the trial as widely as possible. This is likely to be through a publication in a peer-reviewed journal, and through presentations at National and International Cardiology conferences.

18. Trial organisation

18.1. Trial and logistics management

The UK Clinical Research Collaboration accredited LSHTM CTU will be responsible for management for the trial, statistical analysis, database design, data collection and ensuring the trial is run to Good Clinical Practice (GCP) standard.

18.2. Trial steering committee

The Trial Steering Committee (TSC) is responsible for approving the trial protocol, monitoring trial progress and maintaining the scientific integrity of the trial through consultations and updates.

Dr Mark De Belder (Chair) - Independent Cardiologist

Prof Simon Redwood (Chief Investigator) - Cardiologist

Prof Nick Curzen - Independent Cardiologist

Dr Dawn Adamson - Independent Cardiologist

Dr Lucy Blows - Independent Cardiologist

Mr Garth Lane - Independent patient representative

Mr Michael Connor - Independent patient representative

Dr Tiffany Patterson – NIHR Academic Clinical Lecturer/ Specialist Registrar in Cardiology

Mr Mark Whitbread - Consultant Paramedic at LAS

Observers:

Mr Alexander Perkins - Trial Manager

Mrs Rosemary Knight - Senior Manager of the Clinical Trials Unit

Mrs Karen Wilson - Cardiovascular Research Matron

Dr Shannon Amoils - BHF representative

Mr Tim Clayton - Associate Professor, LSHTM

Mr Richard Evans - Senior Manager of the Clinical Trials Unit

18.3. Project management group

Prof Simon Redwood - Chief Investigator / Cardiologist

Dr Tiffany Patterson - Specialist Registrar in Cardiology

Mrs Karen Wilson - Cardiovascular Research Matron

Mr Alexander Perkins - Trial Manager

Mr Richard Evans - Senior Manager of the Clinical Trials Unit

Mrs Rosemary Knight - Senior Manager of the Clinical Trials Unit

Mr Tim Clayton - Associate Professor, LSHTM

Mr Mark Whitbread - Consultant Paramedic at LAS

Dr Joanne Nevett - Clinical Advisor to the Medical Director of LAS

Dr Rachael Fothergill - LAS Head of CARU

Miss Johanna Hughes - LAS Paramedic Research Fellow

18.4. Data and safety monitoring committee

Dr Rod Stables (Chair) - Independent Cardiologist

Prof Douglas Chamberlain - Independent Member

Mr Tim Morris - Independent Statistician

19. References

1. Perkins, G.D., S.J. Brace-McDonnell, and O.P. Group, *The UK Out of Hospital Cardiac Arrest Outcome (OHCAO) project*. *BMJ Open*, 2015. **5**(10): p. e008736.
2. Perkins, G.D. and M.W. Cooke, *Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators*. *Emerg Med J*, 2012. **29**(1): p. 3-5.
3. Sunde, K., et al., *Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest*. *Resuscitation*, 2007. **73**(1): p. 29-39.
4. Carr, B.G., et al., *Inter-hospital variability in post-cardiac arrest mortality*. *Resuscitation*, 2009. **80**(1): p. 30-4.
5. Laver, S., et al., *Mode of death after admission to an intensive care unit following cardiac arrest*. *Intensive Care Med*, 2004. **30**(11): p. 2126-8.
6. Nichol, G., et al., *Regional systems of care for out-of-hospital cardiac arrest: A policy statement from the American Heart Association*. *Circulation*, 2010. **121**(5): p. 709-29.
7. Nichol, G., et al., *Regional variation in out-of-hospital cardiac arrest incidence and outcome*. *JAMA*, 2008. **300**(12): p. 1423-31.
8. Wnent, J., et al., *Choice of hospital after out-of-hospital cardiac arrest--a decision with far-reaching consequences: a study in a large German city*. *Crit Care*, 2012. **16**(5): p. R164.
9. Zive, D., et al., *Variation in out-of-hospital cardiac arrest resuscitation and transport practices in the Resuscitation Outcomes Consortium: ROC Epistry-Cardiac Arrest*. *Resuscitation*, 2011. **82**(3): p. 277-84.
10. Birkmeyer, J.D., et al., *Surgeon volume and operative mortality in the United States*. *N Engl J Med*, 2003. **349**(22): p. 2117-27.
11. Sasson, C., et al., *Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis*. *Circ Cardiovasc Qual Outcomes*, 2010. **3**(1): p. 63-81.
12. Graf, J., et al., *Health care costs, long-term survival, and quality of life following intensive care unit admission after cardiac arrest*. *Crit Care*, 2008. **12**(4): p. R92.
13. Petrie, J., et al., *Hospital costs of out-of-hospital cardiac arrest patients treated in intensive care; a single centre evaluation using the national tariff-based system*. *BMJ Open*, 2015. **5**(4): p. e005797.
14. van Alem, A.P., et al., *Health system costs of out-of-hospital cardiac arrest in relation to time to shock*. *Circulation*, 2004. **110**(14): p. 1967-73.
15. Acker, J.E., 3rd, et al., *Implementation strategies for emergency medical services within stroke systems of care: a policy statement from the*

- American Heart Association/American Stroke Association Expert Panel on Emergency Medical Services Systems and the Stroke Council. Stroke, 2007. 38(11): p. 3097-115.*
16. Cameron, P.A., et al., *A statewide system of trauma care in Victoria: effect on patient survival. Med J Aust, 2008. 189(10): p. 546-50.*
 17. Jacobs, A.K., *Regional systems of care for patients with ST-elevation myocardial infarction: being at the right place at the right time. Circulation, 2007. 116(7): p. 689-92.*
 18. Kern, K.B., *Cardiac receiving centers: beyond hypothermia. Curr Opin Crit Care, 2012. 18(3): p. 246-50.*
 19. Lurie, K.G., A. Idris, and J.B. Holcomb, *Level 1 cardiac arrest centers: learning from the trauma surgeons. Acad Emerg Med, 2005. 12(1): p. 79-80.*
 20. Nolan, J.P., et al., *Advances in the hospital management of patients following an out of hospital cardiac arrest. Heart, 2012. 98(16): p. 1201-6.*
 21. Merchant, R.M., et al., *Cost-effectiveness of therapeutic hypothermia after cardiac arrest. Circ Cardiovasc Qual Outcomes, 2009. 2(5): p. 421-8.*
 22. Neumar, R.W., et al., *Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation, 2008. 118(23): p. 2452-83.*
 23. Noc, M., et al., *Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European association for percutaneous cardiovascular interventions (EAPCI)/stent for life (SFL) groups. EuroIntervention, 2014. 10(1): p. 31-7.*
 24. Peberdy, M.A., et al., *Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation, 2010. 122(18 Suppl 3): p. S768-86.*
 25. Peberdy, M.A., et al., *Impact of percutaneous coronary intervention performance reporting on cardiac resuscitation centers: a scientific statement from the American Heart Association. Circulation, 2013. 128(7): p. 762-73.*

26. Spaulding, C.M., et al., *Immediate coronary angiography in survivors of out-of-hospital cardiac arrest*. N Engl J Med, 1997. **336**(23): p. 1629-33.
27. Dumas, F., et al., *Emergency Percutaneous Coronary Intervention in Post-Cardiac Arrest Patients Without ST-Segment Elevation Pattern: Insights From the PROCAT II Registry*. JACC Cardiovasc Interv, 2016. **9**(10): p. 1011-8.
28. Dumas, F. and T.D. Rea, *Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm*. Resuscitation, 2012. **83**(8): p. 1001-5.
29. Engdahl, J., et al., *Is hospital care of major importance for outcome after out-of-hospital cardiac arrest? Experience acquired from patients with out-of-hospital cardiac arrest resuscitated by the same Emergency Medical Service and admitted to one of two hospitals over a 16-year period in the municipality of Goteborg*. Resuscitation, 2000. **43**(3): p. 201-11.
30. Kern, K.B. and O. Rahman, *Emergent percutaneous coronary intervention for resuscitated victims of out-of-hospital cardiac arrest*. Catheter Cardiovasc Interv, 2010. **75**(4): p. 616-24.
31. Langhelle, A., et al., *In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway*. Resuscitation, 2003. **56**(3): p. 247-63.
32. Reynolds, J.C., et al., *Coronary angiography predicts improved outcome following cardiac arrest: propensity-adjusted analysis*. J Intensive Care Med, 2009. **24**(3): p. 179-86.
33. Nielsen, N., et al., *Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest*. N Engl J Med, 2013. **369**(23): p. 2197-206.
34. Padosch, S.A., K.B. Kern, and B.W. Bottiger, *Therapeutic hypothermia after cardiac arrest*. N Engl J Med, 2002. **347**(1): p. 63-5; author reply 63-5.
35. Nikolaou, N.I., et al., *Part 5: Acute coronary syndromes: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations*. Resuscitation, 2015. **95**: p. e121-46.
36. O'Gara, P.T., et al., *2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*. Circulation, 2013. **127**(4): p. 529-55.

37. Steg, P.G., et al., *ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation*. Eur Heart J, 2012. **33**(20): p. 2569-619.
38. O'Connor, R.E., et al., *Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*. Circulation, 2010. **122**(18 Suppl 3): p. S787-817.
39. Patterson, T., et al., *A Randomised tRial of Expedited transfer to a cardiac arrest centre for non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest: The ARREST pilot randomised trial*. Resuscitation, 2017.
40. Dumas, F., et al., *Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac Arrest) registry*. Circ Cardiovasc Interv, 2010. **3**(3): p. 200-7.
41. Franzosi, M.G., et al., *Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 study. The GISSI Investigators*. Circulation, 1998. **98**(24): p. 2659-65.
42. Pattinson, S.D., *Emergency research and the interests of participants*. Medical Law International, 2012. **12**: p. 121-141.
43. GMC, *Good practice in Research and Consent to Research*. 2010.
44. Mason, S., et al., *Brief report on the experience of using proxy consent for incapacitated adults*. J Med Ethics, 2006. **32**(1): p. 61-2.
45. Callaway, C.W., et al., *Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*. Circulation, 2015. **132**(18 Suppl 2): p. S465-82.
46. Sandroni, C., et al., *Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine*. Intensive Care Med, 2014. **40**(12): p. 1816-31.
47. Camuglia, A.C., et al., *Cardiac catheterization is associated with superior outcomes for survivors of out of hospital cardiac arrest: review and meta-analysis*. Resuscitation, 2014. **85**(11): p. 1533-40.
48. Claxton, K., *The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies*. J Health Econ, 1999. **18**(3): p. 341-64.
49. Fenwick, E. and S. Byford, *A guide to cost-effectiveness acceptability curves*. Br J Psychiatry, 2005. **187**: p. 106-8.

50. van Hout, B.A., et al., *Costs, effects and C/E-ratios alongside a clinical trial*. *Health Econ*, 1994. **3**(5): p. 309-19.
51. Pattinson, S.D., *The value of bodily material: acquiring and allocating human gametes*. *Med Law Rev*, 2012. **20**(4): p. 576-603.
52. Pocock, S.J., T.C. Clayton, and G.W. Stone, *Challenging Issues in Clinical Trial Design: Part 4 of a 4-Part Series on Statistics for Clinical Trials*. *J Am Coll Cardiol*, 2015. **66**(25): p. 2886-98.

Appendix A: List of sites and Principal Investigators

London Ambulance Service

LAS is responsible for identification, randomisation and delivering the trial treatment.

Site	Principal Investigator
London Ambulance Service	<i>Mr Mark Whitbread</i>

CAC Sites

Site	Principal Investigator
St Thomas Hospital	<i>Professor Simon Redwood</i>
St Barts' Heart Centre	<i>Dr Miles Dalby</i>
King's College Hospital	<i>Professor Philip MacCarthy</i>
Harefield Hospital	<i>Dr Ajay Jain</i>
St George's Hospital	<i>Dr Zoe Astroulakis</i>
Royal Free Hospital	<i>Dr Roby Rakhit</i>
Hammersmith Hospital	<i>Dr Iqbal Malik</i>

Emergency Departments

The following sites will receive patients randomised to control only.

Site	Principal Investigator
St Thomas' Hospital (ED only)	<i>Professor Simon Redwood</i>
King's College Hospital (ED only)	<i>Professor Philip MacCarthy</i>
Harefield Hospital (ED only)	<i>Dr Ajay Jain</i>
St. George's Hospital (ED only)	<i>Dr Zoe Astroulakis</i>
Royal Free Hospital (ED only)	<i>Dr Roby Rakhit</i>
Hammersmith Hospital (ED only)	<i>Dr Iqbal Malik</i>
Barnet Hospital	<i>TBC</i>
Northwick Park Hospital	<i>TBC</i>
Hillingdon Hospital	<i>TBC</i>
Queens Hospital, Romford	<i>TBC</i>
University College Hospital	<i>TBC</i>
Homerton Hospital	<i>TBC</i>
Ealing Hospital	<i>TBC</i>

Queen Elizabeth Hospital	<i>TBC</i>
North Middlesex Hospital	<i>TBC</i>
West Middlesex Hospital	<i>TBC</i>
Whittington Hospital	<i>TBC</i>
Kingston Hospital	<i>TBC</i>
Lewisham Hospital	<i>TBC</i>
St Helier Hospital	<i>Dr Richard Bogle</i>
Newham Hospital	<i>TBC</i>
St Mary's Hospital	<i>TBC</i>
King George Hospital	<i>TBC</i>
Charing Cross Hospital	<i>TBC</i>
Chelsea and Westminster Hospital	<i>TBC</i>
Princess Royal Hospital	<i>TBC</i>
Croydon University Hospital	<i>TBC</i>
Darent Valley Hospital	<i>TBC</i>
Watford Hospital	<i>TBC</i>
Royal London Hospital	<i>TBC</i>
Whipps Cross Hospital	<i>TBC</i>

Appendix B: EQ-5D-5L



Health Questionnaire

English version for the UK

ARREST Trial Number:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Date of Birth:	<input type="text"/> d <input type="text"/> d <input type="text"/> m <input type="text"/> m <input type="text"/> y <input type="text"/> y <input type="text"/> y <input type="text"/> y
Follow Up:	30 days <input type="checkbox"/> 12 months <input type="checkbox"/>



EQ-5D-5L



ARREST Trial Number:

--	--	--	--	--	--	--	--

Date completed

d	d	m	m	y	y	y	y
---	---	---	---	---	---	---	---

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

Mobility

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

Self-Care

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

Anxiety / Depression

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

EQ-5D-5L

ARREST Trial Number:

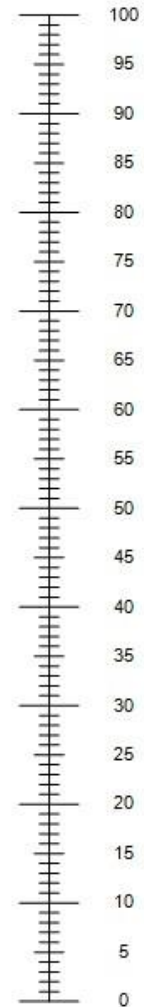
--	--	--	--	--	--	--	--



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the **best** health you can imagine.
- 0 means the **worst** health you could imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

