JRMO Research Protocol for Interventional Studies

Full Title	Feasibility study of a pre-hospital extra-corporeal membrane oxygenation (ECMO) capable advanced resuscitation team at achieving blood flow within 30 minutes in patients with refractory cardiac arrest.
Short title	The Sub30 feasibility trial
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1. Glossary and abbreviations

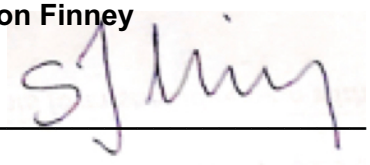
AE	Adverse Event
ALS	Advanced Life Support
APP	Advanced Paramedic Practitioner
CI	Chief Investigator
CPR	Cardiopulmonary resuscitation
CRF	Case Record Form
CTU	Clinical Trials Unit
CVCTU	Cardiovascular Clinical Trials Unit
DSMC	Data Safety and Monitoring Committee
ECMO	Extra-Corporeal Membrane Oxygenation
ECPR	Extracorporeal Cardiopulmonary Resuscitation
ED	Emergency Department
FIM	Functional Independence Measure
GCP	Good Clinical Practice
ICU	Intensive Care Unit
ISF	Investigator Site File
JRMO	Joint Research Management Office (Barts Health/QMUL)
LAS	London Ambulance Service
NHS	National Health Service
NIMP	Non-investigational Medicinal Product
OHCA	Out-of-hospital Cardiac Arrest
PEA	Pulseless electrical activity
PI	Principal Investigator
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
ROSC	Return of spontaneous circulation
SAE	Serious adverse event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TMF	Trial Master File
TOR	Terms of reference
TSC	Trial Steering Committee
UK	United Kingdom
VA-ECMO	Veno-arterial-ECMO
VF	Ventricular fibrillation
VT	Ventricular tachycardia

2. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol (Version 4.0, dated 13 July 2020) will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations.

Chief Investigator Name: **Simon Finney**

Signature: 

Date: **02 March 2022**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: **Thomas Godec**

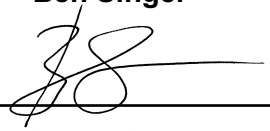
Signature: 

Date: **02 March 2022**

Principal Investigator's Agreement

The study as detailed within this research protocol (Version 4.0, dated 13 July 2020) will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations.

Principal Investigator Name: **Ben Singer**

Signature: 

Date: **02 March 2022**

3. Summary and synopsis

Short Title	Sub30
Methodology	Feasibility study of a complex intervention
Research Sites	Barts Health NHS Trust London Ambulance Service NHS Trust
Objective/Aims	To establish whether a pre-hospital advanced physician/ paramedic cardiac arrest team that is ECMO capable can establish ECMO flow within 30 minutes of collapse
Number of participants	6 patients who are cannulated for ECMO
Inclusion and exclusion criteria	Male and female patients with a known or visible age of 18 to 65 years who: • have a witnessed out-of-hospital cardiac arrest • a presumed cardiac aetiology to their cardiac arrest • receive bystander chest compressions within 3 minutes • remain in cardiac arrest at 20 minutes following collapse or fail to sustain ROSC in the pre-hospital setting The following patients will not be suitable for ECMO: • Identified as or visibly less than 18 years or greater than 65 years • Known or visible advanced pregnancy (when resuscitative hysterotomy should be performed) • Evidence from others present at the scene or patient examination that ECMO unlikely to benefit patient (e.g. advanced frailty, advanced malignancy, …). • No signs of life (physical movement or breathing) AND evidence of ineffective chest compressions suggested by: – Absence of electrical activity OR – End tidal carbon dioxide level of less than 1.3 kPa (10 mmHg) Out-of-hospital cardiac arrest encompasses both those who arrest prior to the emergency services being called and those who are witnessed to arrest by the emergency services. For the purpose of this study patients who suffer their first cardiac arrest whilst in transit to hospital will not be included.
Statistical methodology and analysis	Descriptive statistics will be presented summarising the process and outcomes of the six patients. Outcomes will be compared to other patients who were managed by London Ambulance Service on non-study days. Statistical matching to patients cared for concurrently with the study period will utilise a priori defined factors that may be associated with likely suitability for ECPR. Statistical matching will be individual, propensity score based and GenMatch guided.
Proposed start date	01 June 2019
Proposed end date	31 December 2022
Study duration	3 years 7 months

4. Introduction

4.1 Out of hospital cardiac arrest – the healthcare need

In England, 91% of patients with out-of-hospital cardiac arrest died before leaving hospital in 2015 [1]. Within London, the London Ambulance Service (LAS) attended 10,116 out-of-hospital cardiac arrests (OHCA) in 2015/16 and attempted resuscitation in 4,389. Overall mortality was 91% for those in whom resuscitation is attempted [2]. Survival rates remain low despite improved bystander cardiopulmonary resuscitation (CPR), improved access to defibrillators, the introduction of automated compression devices and the introduction of advanced paramedic practitioners. Even among the subset most likely to survive ("Utstein comparator group" – bystander witnessed cardiac arrests with a shockable rhythm), 35.5% (199/560 in 2015/2016) of patients failed to achieve return of circulation and the overall mortality was 68.5% (371/542). The mortality for those patients with witnessed cardiac arrests but in a non-shockable rhythm was 97.5% (3,353/3,440).

4.2 Rationale for pre-hospital ECPR

4.2.1 ECPR may improve outcome in refractory cardiac arrest

Poor survival from out of hospital cardiac arrest relates to an irreversible decline in cardiac function and/or ischaemic injury to the rest of the body, particularly the brain.

In 2015/16, 70% of all cases and 36% of the Utstein comparator group failed to achieve and sustain a return of a spontaneous circulation (ROSC) [2]. Failure to achieve sustained ROSC is a consequence of the precipitating pathology, insufficient coronary perfusion pressure generated by external chest compressions [3], significant cardiac dysfunction during transient ROSC, and the cardiac contusion from prolonged CPR. Failed or delayed ROSC delays treatment at the heart attack centre or Emergency Department (ED), and prolongs the "low blood flow" state - external chest compressions only generate a flow of ~0.6 $L.min^{-1}.m^{-2}$, less than one-third of normal cardiac output [4]. This "low flow" state perpetuates organ ischaemia multi-organ failure and hypoxic brain injury - the leading causes of death in the two thirds of patients who die in hospital despite achieving ROSC.

Veno-arterial Extra-Corporeal Membrane Oxygenation (VA-ECMO) is a supportive technique that provides an effective circulation of oxygenated blood, over 2 $L.min^{-1}.m^{-2}$ – far superior to external cardiac massage even with mechanical devices. VA-ECMO is performed by inserting a cannula into a large vein to all blood to be pumped from the patient through a membrane oxygenator (that removes carbon dioxide and adds oxygen) and then back to the patient via another cannula inserted into an artery. In this way, it supports both the heart and lungs, limiting organ ischaemia and allowing time for the definitive treatment at the heart attack centre. Moreover, VA-ECMO favourably influences myocardial oxygenation by enhancing coronary perfusion through an increased mean arterial pressure and reduced ventricular filling pressures coupled with a normalisation of acid-base abnormalities and often a reduction in cardiac work. Excessive mean arterial pressures may increase cardiac work and are avoided. This may limit on-going cardiac damage and is an emerging concept ("door to unloading time") in the management of ST elevation myocardial infarction complicated by cardiogenic shock [5].

VA-ECMO is employed in a variety of clinical settings, but when used in cardiac arrest is termed Extracorporeal Cardio-Pulmonary Resuscitation (ECPR). The use of ECPR for in-hospital cardiac arrest is associated with a stepwise improvement in survival to hospital discharge depending on how rapidly ECPR is established: 40-50% for ECPR within 30 minutes of collapse, 30% for ECPR within 30-60 minutes, and 18% for ECPR beyond 60 minutes [6]. ECPR has also been used in out of hospital cardiac arrest, but is typically instituted in the ED. Transporting the patient to hospital delays ECPR, and the reported survival rates are typically lower at around 17% [7]. A recent case series published survival to discharge rates as high as 54% in a mix of in- and out- of hospital cardiac arrest patients, but the average time in survivors from collapse to ECPR was 40 minutes [8].

ECPR has never been investigated in randomised controlled trial.

4.2.2 Pre-hospital institution of ECPR may be the best model of care

Time to establish an adequate circulation is critical both in ECPR and conventionally managed cardiac arrest [6, 9-12]. The time taken to package and transport patients, after the required minimum of 20 minutes of advanced life support (ALS) on scene following OHCA, means that the earliest it is possible to institute ECPR in heart attack centres and EDs is approximately 60 minutes after arrest, the time at which survival starts to fall significantly. Pre-hospital ECPR instituted where the patient suffers a cardiac arrest may reduce this time interval.

The technical feasibility of pre-hospital ECPR has been demonstrated [13-16]. The logistic challenges of delivering a complex medical intervention in the pre-hospital setting are significant. They include identifying and reaching appropriate patients as soon as possible after their cardiac arrest, establishing a sterile field, accessing femoral veins and arteries during active resuscitation attempts, and managing a pre-hospital scene with all the potential environmental challenges.

The Parisian experience with pre-hospital ECPR is an excellent model to illustrate potential pitfalls. When pre-hospital ECPR was first introduced in Paris, the mean interval between collapse and ECPR was 79 minutes [15]. The ECPR team acted as a secondary response, deployed only after initial on-scene assessment by the primary responders, and mandatory conventional resuscitation for 30 minutes. Not surprisingly, these delays were associated with poor outcomes. Since then, they have refined their eligibility criteria and focused on faster dispatch to the scene. These modifications have translated into both shorter collapse-to-ECPR intervals and significantly improving clinical outcomes [17].

4.3 Current UK clinical practice for OHCA

Most ambulance services in England follow the European Resuscitation Council guidelines for pre-hospital resuscitation [18], which advise at least 20 minutes of CPR for all attempted resuscitations. If there is failure to achieve ROSC and the cardiac rhythm is asystole, then the resuscitation is terminated, typically. Resuscitation may also be stopped if the cardiac rhythm is pulseless electrical activity (PEA) after discussion with a clinical support desk. If the rhythm is refractory ventricular fibrillation/tachycardia (VF/VT), the patient will be transported with on-going CPR to the nearest emergency department or heart attack centre.

Hospital based ECPR is provided in a few EDs and heart attack centres throughout England on an ad-hoc, case-by-case basis. The UK Resuscitation Council 2015 guidelines recommend that ECPR should be considered as a rescue therapy for select patients in whom initial ALS techniques are unsuccessful [19]. There is no national protocol for its use and it has never been performed in a pre-hospital setting in the UK.

4.4 Other current and planned studies of ECPR in patients suffering OHCA

There are six other potential studies examining ECPR in patients suffering OHCA. These are summarised in Table 1. Indeed, a panel of experts recommended a trial of pre-hospital ECMO as a key study to undertake in the next 10 years [20].

The RECA study (Regensburg ECLS for Cardiac Arrest) aims to implement pre-hospital ECPR in patients between 18 and 65 years with witnessed cardiac arrests, of presumed cardiac aetiology (as assumed with a presenting rhythm of VF or VT) who receive bystander/healthcare worker CPR within 5-10 minutes. It is a single centre study run by the Universitätsklinikum Regensburg. The team is being dispatched via the integrated command centre in Regensburg at the same time as the primary response team. The study is not officially registered on any international database and its current status is not known.

ACPAR2 (A Comparative study between a Pre-hospital and in hospital Circulatory support strategy [ECMO] in refractory cardiac ARrest; clinicaltrials.gov reference: NCT02527031) is a randomised controlled trial being run by the Service d'Aide Médicale Urgent (SAMU) in Paris. It began recruiting in March 2016. It aims to recruit 210 patients, aged between 18 and 65 years, who remain in medical cardiac arrest at 20 minutes. It aims to achieve VA-ECMO between 20 and 30 minutes and compare these to patients transferred at 30 minutes to the hospital for ECPR.

Patient exclusions include those who have more than five minutes of collapse without CPR and those with an end tidal carbon dioxide level of less than 10 mmHg (1.3 kPa). It is powered to detect an increase in survival without severe neurological dysfunction from 5 to 20%.

The CHEER3 study from the Alfred Hospital in Melbourne is being planned and aims to commence ECMO cannulation at 30 minutes and aiming to achieve blood flow by 45 minutes using percutaneous cannulation.

EROCA (ECPR for Refractor Out-of-hospital Cardiac Arrest; clinicaltrials.gov reference: NCT03065647) is currently in set up and run by the University of Michigan. It aims to enrol 30 patients over 18 months and compare conventional CPR against ECPR following expedited transfer to hospital with mechanical CPR for ECPR. Expedited transfer commences after the initial cardiac rhythm analysis and shock (if indicated). The primary outcomes are the times to arrival in the ED and ECPR commencing. Target times are arrival at hospital within 30 minutes and an additional 30 minutes to achieve ECPR.

ECPB4OHCA (Emergency Cardiopulmonary Bypass for Cardiac Arrest; clinicaltrials.gov reference: NCT01605409) is a single centre study being undertaken in Vienna. The study aims to randomise 40 patients, aged between 18 and 75 years, to receive conventional CPR or ECPR. In the ECPR group expedited transfer to the hospital is imitated following 15 minutes of standard ALS. The primary outcome is the rate of sustain restoration of the circulation. The study commenced in November 2014.

Prague OHCA study (clinicaltrials.gov reference: NCT01511666) is being undertaken by the Chares University, Prague. Patients, aged 18 to 65 years, suffering witnessed OHCA are randomised to receive in standard of care or a hyper-invasive resuscitation that includes mechanical chest compressions, intra-arrest nasal cooling, and early ECLS invasive assessment. The study aims to achieve ECMO support within 60 minutes and recruit 170 patients. The primary outcome is composite of survival with good neurological outcome at 6 months (Clinical Performance Category of 1-2). The study team is activated as soon as the Emergency Medical Services start to give CPR telephone advice.

Table 1 Other studies examining ECPR in patients suffering OHCA

Study name	Status	Country	Site of ECPR	Technique	Minimum conventional CPR	Target ECPR time
RECA	-[a]	Germany	Pre-hospital	Percutaneous	-[a]	-[a]
CAREECMO	In set up	France	In hospital	Percutaneous	10 min	-
ACPAR2	Recruiting	France	Pre-hospital	Cut-down	20 min	<30 min
CHEER2	Recruiting	Australia	In hospital	Percutaneous	29 min	Start<45
CHEER3	In set up	Australia	Pre-hospital	Percutaneous	30 min	<45 min
EROCA	In set up	USA	In hospital	Not defined	1 shock[b]	<60 min
ECPB4OHCA	Recruiting	Austria	In hospital	Percutaneous	15 min	-
Prague OHCA	Recruiting	Czech Rep.	In hospital	Percutaneous	5 min	<60 min
Sub30	In set up	UK	Pre-hospital	Percutaneous	20 min	<30 min

[a] Details not known

[b] Or one rhythm analysis if a shock is not indicated

4.5 Rationale for the Sub30 study

The Sub30 will investigate the technical and logistical feasibility of instituting pre-hospital ECPR within 30 minutes of collapse for selected patients in a geographical sector of Greater London. It will achieve this through a unique collaboration between the primary emergency dispatch and response services (London Ambulance Service NHS Trust, LAS), pre-hospital practitioners (LAS and London Air Ambulance) and clinicians in ECMO (Barts Health NHS Trust).

A target of thirty minutes to achieve ECMO flow is less than in published series to date. This can be achieved by:

- integration into an established pre-hospital emergency response services that aggressively pursues ROSC through optimised ALS

- immediate deployment of an ECPR-capable cardiac arrest team as a primary resource, as opposed to delayed secondary deployment. Dispatch will be done by the established Advanced Paramedic Practitioner (APP) desk of LAS, with the objective to reach the patient within 8-10 minutes of the 999 call.
- early placement of guide-wires into the femoral vessels during on-going conventional CPR, a procedure with low complication risk that does not commit the team to ECPR but will minimise the delay to ECPR support if conventional resuscitative techniques are not successful within 20 minutes
- facilitated guide-wire placement through real-time wireless ultrasound delivered to the operator through augmented reality smart glasses

Some OHCA are irreversible in nature and ECPR would not provide benefit to these patients. The ECPR team will not be task fixated on providing ECPR, but also supportive of the APP primary responders and provide ECPR only in settings of refractory cardiac arrest that fulfils the study criteria, that have been chosen based on best available evidence to identify those patients in whom ECPR is likely to be of benefit.

If pre-hospital ECMO is feasible within 30 minutes of chest compressions starting, then a larger randomised controlled study of clinical and cost effectiveness is merited. Optimisation of the delivery of ECPR is vital, prior to a controlled study, in order to maximise any potential benefits for patients. Data from Sub30 will inform the design of such studies enabling an estimation of the size of any potential outcome benefits and the likely affordability for a healthcare service. Ideally studies would be international and multi-city to understand the generalisability of pre-hospital ECMO to other urban and non-urban environments.

4.6 Risks / benefits

The potential benefits relate to the restoration of blood flow to vital organs preventing or reducing neurological injury, renal failure, liver failure and cardiac failure. ECPR may also enable a patient to undergo coronary angiography and intervention whilst still in “cardiac arrest”. These may all translate to more patients surviving and survivors having better neurological outcomes.

The potential risks to participants are:

- vascular damage during cannulation. This will be mitigated by the use of ultrasound to guide the operator.
- bleeding. This is related to the administration of anticoagulants to prevent clotting in the extracorporeal circuit. Anticoagulation will be monitored closely during the study. Bleeding is common in the context of ECMO.
- local infection. This may be greater due to the procedure occurring outside the confines of a procedure room in a hospital. The risk of infection will be mitigated by using chlorhexidine skin preparation, allowing it to dry, large drapes to maximise the sterile field and prevent inadvertent contamination a single dose of prophylactic antibiotic directed against common skin commensal organisms.
- individuals, who would have previously died, surviving with neurological impairment

5. Study objectives

The study aims to test the hypothesis that a system that overcomes the logistical and technical barriers to minimise the collapse-to-ECPR interval and combines an ECMO team with advanced pre-hospital practitioners can establish patients in refractory cardiac arrest with ECMO flow (>50% target) within 30 minutes of collapse.

5.1 Primary objective

The primary objective of the study is to assess the ability of an advanced ECMO capable resuscitation team to establish patients on ECPR within 30 minutes of collapse.

5.2 Secondary objectives

The secondary objectives of the study are to assess the logistics of delivering a definitive clinical study of the efficacy of pre-hospital ECPR in terms of:

- the logistics of delivering the study including potential recruitment rates
- the safety of delivery of pre-hospital ECPR
- the survival and neurological outcome of patients included in the feasibility study
- the logistics of collecting data regarding resources used and the health economics

5.3 Primary outcome

The primary endpoint is the proportion of patients successfully established with pre-hospital ECPR within 30 minutes of collapse. The time of collapse will be defined as the time the call to the emergency services commences or the time that a patient was witnessed to suffer a cardiac arrest if this happens in front of the emergency services.

5.4 Secondary outcomes

The following secondary endpoint will be measured:

- number of patients not dispatched to as travel time too great/team unavailable
- number of patients in whom it is attempted to start inserting guidewires but do not meet study inclusion criteria at 20 minute time out.
- the number of patients successfully cannulated between 31 and 45 minutes
- the number of patients successfully cannulated between 46 and 60 minutes
- proportion of patients who achieve ROSC prior to the 20 minutes timeout
- the number of patients in refractory cardiac arrest at 20 minutes in whom ROSC is achieved prior to ECMO flow
- time interval between call to the emergency services and ECPR team arrival
- proportion of potentially supportable patients in whom guidewire placement is attempted
- organ dysfunction during the first five days of hospital stay
- survival to hospital discharge
- neurological outcome at hospital discharge (Cerebral Performance Category and modified Rankin scales)
- incidence of ECPR-related complications (failure to cannulate, vascular injury, site infection and distal leg ischaemia)

Details about resources used and health economic data will be collected to estimate the range of costs and affordability of any subsequent clinical trial or clinical service. These data will include:

- ECMO equipment used
- duration of ECMO support
- duration of intensive care unit stay
- maximum organ support on the Intensive Care Unit (ICU)
- duration of acute hospital stay
- duration of inpatient rehabilitation following acute hospital stay

6. Study population

6.1 Inclusion criteria

Male or female patients with a known or visible age of 18 to 65 years who:

- have a witnessed out-of-hospital cardiac arrest
- a presumed cardiac aetiology to their cardiac arrest
- receive bystander chest compressions within 3 minutes
- remain in cardiac arrest at 20 minutes following collapse or fail to sustain ROSC in the pre-hospital setting

Out-of-hospital cardiac arrest encompasses both those who arrest prior to the emergency services being called and those who are witnessed to arrest by the emergency services. For the purpose of this study patients who suffer their first cardiac arrest whilst in transit to hospital will not be included.

6.2 Exclusion criteria

The following patients will not be suitable for entry into the study:

- Known to be are visibly appear younger than 18 years old or older than 65 years.
- Known or visible advanced pregnancy (when resuscitative hysterotomy should be performed)
- No signs of life (physical movement or breathing) AND evidence of ineffective chest compressions suggested by:
  - absence of electrical activity at 20 minutes time out OR
  - end tidal carbon dioxide level of less than 1.3 kPa (10 mmHg)
- Evidence from others present at the scene or patient examination that ECMO unlikely to benefit patient (e.g. advanced malignancy, severe frailty). The narrative of this decision will be recorded in the Case Record Form (CRF).

7. Study design

7.1 Overall design

The study is a feasibility study of a complex intervention performed on two study sites.

7.2 Setting and timescale

The study will be undertaken in North East London over approximately 12 months. The study site is Barts Health NHS Trust.

7.3 Timescale

The study will only be performed on study days when the ECMO team is available. It is anticipated that this will be 2-3 days per week. It is anticipated that it will take up to 52 study days to recruit six patients.

7.4 Patient identification / ECPR Team activation

On study days, the ECPR team will be active in a fast response blue light emergency response car provided by London's Air Ambulance. They will have no other clinical or non-clinical duties. On study days, the team will assemble at the Royal London Hospital and perform challenge/response checks on their equipment and vehicle. Once complete they will inform control that they are active and available. At various points in the day the team will be based in geographical areas where London Ambulance Service have attended the most cardiac arrests historically. At the end of the shift the team will inform control that they are standing down.

The team will be activated by the Advanced Paramedic Practitioner (APP) desk in the Emergency Operations Centre at London Ambulance Service. This desk screens in real time all calls to the emergency services that may be a cardiac arrest and dispatch additional APPs to the scene. They listen in on all calls where it is indicated on the pre-triage questions, asked by the call handler, that the patient is not breathing or has abnormal breathing. In addition, they screen calls as requested by the dispatchers. Their clinical experience at listening to calls will enable the LAS sit to identify trial subjects and dispatch the ECPR team as an additional emergency response within 2-3 minutes of the emergency call being placed. They will task the ECPR team if the estimated time of travel to the scene is 20 minutes or less.

All 'patients' for whom the team is activated will be included in the screening log. In addition to patients who are enrolled and receive ECMO, the log will indicate those people who were never assessed (as the team was stood down prior to arrival), those whose were assessed but clearly

did not meet inclusion/exclusion criteria (Section 8.2) and those in whom guidewires were inserted but were not formally enrolled in the study at the 20 minute time out (Section 8.5)

7.5 Consent waiver at enrolment

Patients are unable to provide consent to enter the study at the point of enrolment as they lack capacity since they are unconscious and in cardiac arrest. This situation is sudden and unexpected preventing prior consultation with the patient and prospective consent. Their capacity will not vary throughout the intervention period as they will remain in cardiac arrest and unconscious. Since there are no alternative groups of patients in whom this study could be conducted it is necessary to recruit patients who lack capacity.

It is unlikely that if it were possible to consult a personal consultee, in the context of the distress of learning the patient is in cardiac arrest, that any such person could be able to make an informed decision in the limited time available.

Since delays in resuscitation and emergency treatments are associated with worse patient outcomes, it is not practical in this study to consult a professional consultee, such as their general practitioner, without placing the participant at potential harm from delayed treatment.

Therefore, patients will be enrolled without specific consent at the start of the study if they meet eligibility criteria. This was specifically discussed at a patient and public engagement event (Section 12) and was considered universally acceptable by the attendees.

If a patient is wearing a MedicAlert bracelet that indicates they have indicated an Advance Decision about their care, and there is sufficient time to find out about the Advance Decision then this will be undertaken and respected if the Decision is considered to be valid and within the context of the clinical scenario. An indication by a patient that they would not wish to receive blood products will not preclude them receiving ECPR. Any Advance Decisions will be discussed with the Barts Health NHS Trust legal time at the earliest opportunity.

7.6 Consent to on-going inclusion in the study

ECMO support will be life-sustaining. A personal consultee will not be asked if the participant should remain in the study. Nevertheless, they will be consulted about the patient's other medical conditions and likely wishes and these will be considered, according to standard clinical practice, by the attending physicians who will not be study investigators. Family and friends of study participants will be given information about the study as soon as is practicable.

Participants will be approached if they regain capacity to inform them of their participation in the study. This will be done prior to hospital discharge and usually on the hospital ward when they are no longer critically unwell. Individual patients can ask to be withdrawn from the study if they request to do so. Data already collected will be processed. The legal basis for processing these data, which include special category data, is as a task in the public interest as outlined in General Data Protection Regulation and the Data Protection Act (2018). Patients will not be required to provide a reason for wanting to withdraw from the study. Withdrawal will not influence the goals of on-going medical care for a patient.

7.7 Provision of public information about the study

We will disseminate information about the study through LAS, Barts Health, and London Air Ambulance. Media used for information will include the internet, newsletters, posters, annual reports and discussion at public meetings. The public will be directed to the trial website for further information.

People will be able to decline participation in the trial in the event they sustain a cardiac arrest. Requests not to participate will be sent to the Chief Investigator who will ensure a that a stainless steel "No Sub30 study" bracelet is issued to the person's home address.

7.8 Co-enrolment in other clinical studies

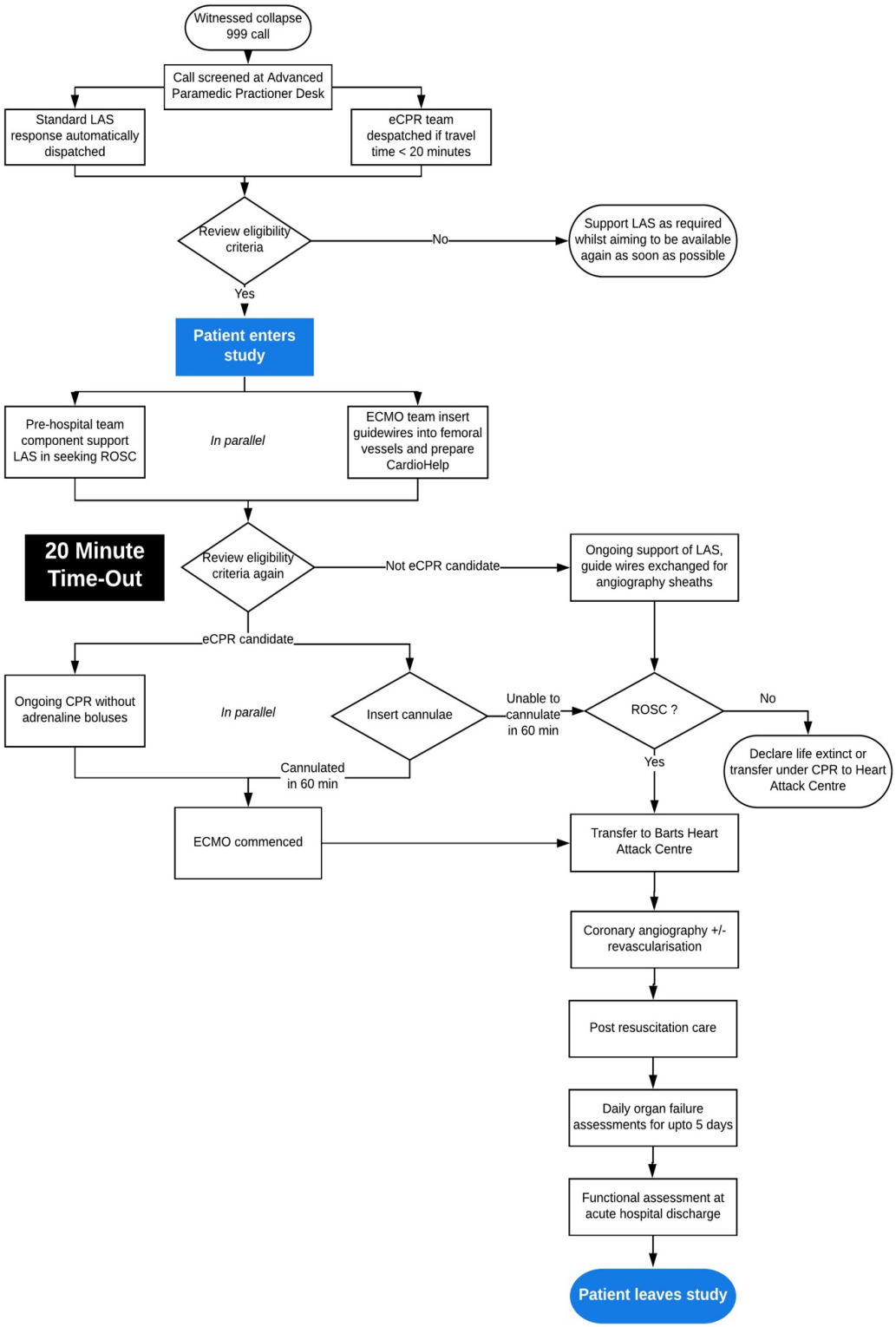
Patients in Sub30 are eligible for co-enrolment in other studies and the scientific validity of this will be decided by the Chief Investigator on a case by case basis in keeping with the UK guidelines for critical care research [21]. Co-enrolment with any studies should be documented in the CRF.

7.9 End of study

The end of the study is defined as 90 days after the final patient is recruited into the study.

The study will be discontinued early if the sponsor or Data Safety and Monitoring Committee request the study to be stopped. The Trial Steering Committee will advise how to manage patients receiving ECMO as study participants when this decision is made.

7.10 Study Scheme Diagram



8. Study procedures

The delivery of pre-hospital ECMO is a complex procedure that encompasses dispatch of the ECPR team to the patient, assessment, institution of ECMO, transfer to Heart Attack Centre and then on-going care at the Heart Attack Centre in the cardiac catheterisation laboratory, intensive care unit and ward. Full details are provided in the latest approved version of the Study Manual. This section contains a synopsis of the key aspects of care.

8.1 ECPR Team members

The ECPR team will comprise of:

- A pre-hospital emergency medicine consultant
- An advanced paramedic practitioner/Helicopter emergency medical paramedic
- Two ECMO consultant as defined in the St Bartholomew's Hospital Local Policy for Accreditation of medical and nursing staff as ECMO specialists (SBH-POL-01-2016-012 or any superseding version)

Only the ECMO consultants will perform the ECMO intervention on the study subjects (Sections 8.6 and 8.7), and the other members of the ECPR team as detailed in Section 8.3 are available for medical support, but will act as observers in relation to ECMO management.

8.2 Primary assessment

All team members will follow the current Barts Health NHS Trust and London Ambulance Service NHS Trust procedures regarding protection of patients and staff from SARS-CoV-2 infection. On arrival at the scene the ECPR team will assess whether the inclusion criteria or exclusion criteria are met. They will also undertake a comprehensive bilateral assessment of the pupillary response to light using an automated pupillometer (NPI-200, NeurOptics, Irvine, California).

If the inclusion and exclusion criteria are definitely not met they will:

- Assist alternative LAS resources present on scene as required. Once assistance is no longer required the ECPR team will stand down and inform control that they are available for further tasking to cardiac arrests.
- Provide the primary response, if there are no LAS resources on site, irrespective if the patient is in cardiac arrest or not. They will use standard LAS treatment protocols. Upon arrival of alternative LAS resource then the ECPR team will hand over care of the patient to that resource and stand down unless on-going assistance is required by LAS. On standing down the ECPR team will indicate to control that they are available for further tasking to cardiac arrests.

If inclusion criteria are met and no immediate exclusion criteria identified, then ECPR pre-hospital team members (Pre-hospital medicine consultant and paramedic) will split from the two ECMO consultants who will concurrently fulfil their roles and responsibilities.

8.3 ECPR Pre-hospital team roles and responsibilities

The pre-hospital ECPR team will endeavour to achieve ROSC by delivering and supporting others in delivery of ALS to the patient. They will:

- introduce the ECPR team to any on scene healthcare resources
- manage the cardiac arrest following London Ambulance Service and Resuscitation Council ALS Guidelines
- seek ROSC by addressing reversible causes, ensuring advanced airway management and optimising resuscitation including automated mechanical compressions
- administer intravenous fluids to aid percutaneous cannulation by the ECMO team as required
- manage the pre-hospital environment and ensure team safety
- establish 360 degrees access to the patient
- establish collateral history about the patient, the collapse, and the timings of resuscitation attempts
- prepare for team timeout if cardiac arrest is refractory at 20 minutes of resuscitation by healthcare professionals

8.4 ECMO consultants' initial roles and responsibilities

The ECMO consultants will establish a sterile surgical area in the patient's groin and using real-time ultrasound guidance to percutaneously insert guide wires into the patient's femoral artery and vein. The position of wires in the aorta and inferior vena cava respectively will be confirmed using

subcostal/trans-hepatic ultrasound. They will also complete the priming of the CardioHelp circuit so it is ready for use. If chest compressions must be interrupted for insertion of the needle/guidewire then this will be for no more than ten seconds (as timed by the consultant in pre-hospital medicine) and attempts made to coordinate these with any pulse checks.

If ROSC is achieved prior to 20 minutes of resuscitation then any wires present at that point will be used to insert 6Fr angiography sheaths into the femoral artery and/or vein to facilitate care at the Heart Attack Centre. The team will then continue to support LAS as required to provide standard post-resuscitation care and expedited transfer to the nearest Heart Attack Centre.

8.5 Twenty minute time-out if patients remains in cardiac arrest

Twenty minutes after the start of resuscitation by a healthcare provider a team time out will be called. Cardiopulmonary resuscitation will continue during this time out.

The pre-hospital consultant will present the patient using the Situation Background Assessment Recommendation (SBAR) format. The assessment will include reciting the inclusion and exclusion criteria in a challenge response manner. If the team considers that there are no exclusion criteria met then the ECMO consultants will proceed to cannulate the patient's femoral artery and vein and commence ECMO support. In the interval between 20 minutes of resuscitation and ECMO support, no more epinephrine (adrenaline) boluses will be administered. If chest compressions must be interrupted for insertion of the cannulae then this will be for no more than ten seconds (as timed by the consultant in pre-hospital medicine).

If an exclusion criterion is identified then any wires present at that point will be used to insert 6 Fr angiography sheaths into the femoral artery and/or vein which may facilitate on-going care. The team will then continue to support LAS as required. All patients will be followed up for adverse events related to the insertion of guidewires for seven days following the cardiac arrest. No other data, other than that included in the screening log, will be collected for these patients.

If cannulation cannot be achieved within 60 minutes then further attempts will not be continued and the patient reviewed and consideration made to declare life extinct or transport the patient under ongoing CPR to the nearest emergency department.

8.6 ECMO support

Target parameters for initial ECMO support and the on-going care of the patient on ECMO are outlined in the ECMO Study Manual. ECMO support will endeavour to ensure perfusion of the vital organs whilst minimising any reperfusion injury and be based on any clinical and preclinical data available.

8.7 Transfer to the Heart Attack Centre at St Bartholomew's Hospital

Patients will be transferred to the Heart Attack Centre at St Bartholomew's Hospital by the two ECMO consultants and London Ambulance Service. The Heart Attack Centre will be pre-alerted using the current systems in process that alert the teams as to whether patients are "self-ventilating" or "ventilated". An additional category of "ECMO supported" will be included.

8.8 Post-resuscitation care

Following arrival at the Heart Attack Centre the care of the patient will be managed by standard algorithms outlined in the Study manual. These will essentially follow the Standard Operating Procedures and Policies of St Bartholomew's hospital. These consider:

- assessment of the need for coronary angiography
- complete versus culprit-only revascularisation
- use of intra-aortic balloon counter-pulsation
- use of therapeutic hypothermia
- haemodynamic management on ECMO
- management of distal leg perfusion
- anticoagulation management
- weaning from VA-ECMO

- general intensive care unit care
- neurological assessment

8.9 Schedule of assessments

The time of ECMO blood flow >50% target will be recorded on the CRF.

Many assessments will be made as part of routine clinical practice. These will include computed tomography of the brain, electroencephalograms, somatosensory evoked potentials, markers of kidney, liver, heart and lung function. If these are done, then the results will be recorded in the CRF. They are outlined in Table 2.

In addition, other a variety of physiological, biomarkers, and functional outcome measures, that are not part of routine clinical practice, will be recorded as secondary outcomes for the study as outlined in Table 3.

Table 2 Standard clinical assessments made that will be included in CRF (if undertaken by clinical team)

Assessment	4 h	24 h	Any time point in 7 d
RIFLE score[a]		✓	
Computed tomography of brain			✓
Electroencephalography			✓
Somatosensory evoked potentials			✓
Liver function tests[b]	✓	✓	✓
Echocardiography[c]			✓
Vital signs[d]	✓	✓	
Vasoactive medication use[e]	✓	✓	
Coagulation assessments[f]	✓	✓	

[a] The RIFLE score is a classification of acute kidney injury based on creatinine levels and urine output
[b] Specifically bilirubin, aspartate transaminase, alkaline phosphatase
[c] A comprehensive study as outlined by the British Society of Echocardiography
[d] Including heart rate, blood pressure, right atrial pressure, pulmonary artery occlusion pressure, cardiac output and arterial lactate
[e] Including adrenaline, noradrenaline, dobutamine, dopamine, milrinone, enoximone, levosimendan
[f] Including prothrombin time, activated partial thromboplastin time, fibrinogen, platelet count

Table 3 Non-routine assessments made during the study

Assessment	Pre-ECMO	Time of hospital admission				Hospital discharge	90 days
		0 h	24 h	48 h	72 h		
Bilateral pupillometry	✓	✓	✓	✓	✓		
Serum Neuron Specific Enolase		✓	✓	✓	✓		
Plasma/Serum biobanked	✓	✓	✓	✓	✓		
Modified Rankin Scale						✓	✓
Function Independence Measure						✓	✓
EQ-5D							✓

8.10 Standard Operating Procedures

The most current standard operating procedures of the Cardiovascular Clinical Trials Unit will be adopted for the conduct of this study. Specific operating procedures have been formulated for other trial activities are outlined in Table 4.

Table 4 Trial specific Standard Operating Procedures

Name	Version	Date
Using the Functional Independence Measure (FIM)	1.0	20 Aug 2018
Maintaining chain of custody for trial disposables and medical gases	1.0	20 Aug 2018
Maintaining chain of custody for trial samples	1.0	20 Aug 2018
Assessing patients with the modified Rankin Scale	1.0	20 Aug 2018
Assessing patients with the EQ-5D-5L instrument	1.0	20 Aug 2018

Completion of Case Report Forms	1.0	20 Aug 2018
Environmental monitoring of storage areas	1.0	25 Mar 2019
Media and publicity	1.0	01 Mar 2019

9. Assessment and management of risk

The details of the risk assessment regarding the study and the mitigating factors put in place are outlined in Table 5.

Table 5 Risk assessment and mitigation for Sub30 study

Risk details	Initial Assessment* PSR	PLR	RRN	Mitigating actions	Reassessment PSR	PLR	RRN
Vascular damage during cannulation Large cannula (typically 17-25 Fr) are being inserted into the femoral artery and vein. This may be associated with damage to the vessel and extensive bleeding. Cannulation is likely to be more difficult out of the ICU/operating room due to patient position, weather, and unfamiliar environment	3	3	9	Use of experienced Consultant operators utilising ultrasound for vascular cannulation.	3	2	6
Infection – Local Pre-hospital ECMO is occurring outside a normal operating environment and there is greater risk of environmental contamination of the cannulation site and infection in the patient.	3	3	9	Chlorhexidine preparation of skin. Careful cleaning of cannulation sites on return to hospital environment. Use of prophylactic antibiotics. Aseptic technique. Consideration made for need to re-cannulate at an alternative sterile site on return to Barts Heart Hospital if the access sites were heavily contaminated.	3	2	6
Neurological injury established pre-ECMO Neurological injury may be sustained during the period of cardiac arrest despite bystander CPR.	4	4	16	Use of mechanical compression device to maximise efficacy of chest compressions whilst ECMO instituted. Minimisation of secondary brain injury with avoidance of hyperthermia, consideration of cerebral perfusion pressure, good glycaemic control. In the setting of continued low blood flow further primary brain injury will be minimised by more aggressive cooling. Pre-hospital ECMO is proposed as method of risk reduction for neurological injury in patients who survive.	3	3	9
Bystander interference during cannulation Cannulation will be done surrounded by members of the public and emergency services. Wishing to help they may disrupt the functioning of the cannulation team preventing their effective operation.	3	3	9	Tasking of emergency services to control the environment and bystanders. Utilisation of consultants in pre-hospital care for scene management.	2	1	2
Adverse climate Wind, cold, and rain may make the cannulation difficult.	2	3	6	Use of IPX4 standard equipment if possible to counter effects of rain. Covers utilised for other equipment. Weights for drapes to counter wind Suspension of service if conditions considered too adverse to safely deliver pre-hospital ECMO	2	2	4

Adverse publicity for Trust/Organisations involved An adverse outcome for the patient (severe neurological injury but survival; or death despite significant and prolonged intervention) may be perceived in retrospect as an inappropriate use of healthcare resource (e.g. ICU capacity, blood products).	2	3	6	Discussion with Communications team prior to the event – avoid all public comments until patient outcome known and consent of patient gained. Aim to undertake resuscitation out of public view	2	2	4
Reduced capacity to support other patients Any patient will take up ICU capacity in terms of bed spaces, staffing, and equipment. This may limit the ability to support the work of elective cardiac surgery or emergency respiratory ECMO.	2	3	6	Pre-hospital ECMO team are additional to the standard ECMO team which would not be influenced by the activity. Planning with the theatre schedulers and cardiac surgeons regarding.	2	2	4
Failure to cannulate femoral vessels Expected failure rate of 5-10% of percutaneous cannulation of femoral vessels in cardiac arrest. Failure would negate ability to initiate ECPR.	3	4	12	Experienced consultants, cannulating with the use of ultrasound, Saline fluid infusion to improve vessel size. Augmented reality ultrasound glasses to improve technique. Any failure to cannulate would mean patient would receive standard ongoing care as per LAS resuscitation protocols.	2	4	8
Leg ischaemia – arterial The size of the arterial cannula can impair blood flow to the ipsilateral limb. A distal limb perfusion cannula will be difficult to insert in the pre-hospital environment	3	4	12	Routine insertion of a distal limb perfusing catheter on return to the Barts Health. Use of smaller arterial cannulae (15Fr).	3	2	6
Infection of patients with SARS-CoV-2 There is a risk of healthcare workers infecting the patient. This may occur acutely in the resuscitation and subsequent hospital care but also when the patients are followed up at 90 days.	4	2	8	Research team will wear full respiratory PPE during their attendance at the cardiac arrest and their continuing care until they leave the patient area. Staff at St Bartholomew's hospital wear appropriate PPE for the patient's risk status and never wear less than gloves and surgical face mask for any patient. Research team will be screened for infection (symptoms and temperature) at the start of each shift. Use of video-consultation in follow up (a practice that has been adopted in our critical care service)	4	1	4

Infection of Research Staff with SARS-CoV2 There is a risk of the patient infecting research staff with SARS-CoV-2. Patients with OHCA are more likely to have SARS-CoV-2.	3	2	6	Cleaning and decontamination of LAA fast-response vehicle as part of morning checks Surgical masks to be worn by all team members while in car (except navigator when giving driver instructions on blue lights) Team no longer roaming but based in a (pre-agreed) LAS ambulance station observing all local COVID-19 precautions at said station Formal 'doffing' and decontamination before every patient contact, presuming all patients are a COVID-19 infection risk Consideration of not bringing ECMO equipment and any non-essential equipment into 'Hot zone' near patient until confirmed potential Sub30 patient (Team-leader role to be updated) Additional sealed PPE grab-bag added to equipment and relevant checklists Symptom and temperature check all team members at start of study day If symptoms of COVID-19 develop during a shift then the study day will be cancelled and the team will self-isolate according to current Barts Health NHS Trust guidance. All patients screened for SARS-CoV-2 infection on arrival to hospital, according to Barts Health NHS Trust standard practice. All patients considered to be potentially infected SARS-CoV-3 – so are managed with full aerosol protecting PPE until infectio	3	1	3
Negative impact on staff wellbeing with participation The additional workload or personal risk factors may mean some of the study team no longer wish to participate in the study. Staff are uncomfortable wearing PPE for long periods of time.	3	3	9	Reinforce that all shifts are voluntary and there is no obligation for trained pool to continue in the study. Individual Barts Health NHS Trust COVID-19 risk assessment made prior to any team member joining the study Additional section to shift de-brief form specific to any COVID-19 related concerns or suggestions	2	2	4

* PSR – Potential Severity Rating; PLR – Potential Likelihood Rating; RRN – Risk Rating Number (PSR x PLR)

10. Statistical considerations

10.1 Sample size

This is a single group study. No power calculation has been undertaken. The estimated sample six patients in whom cannulation is attempted following the twenty minute time out (see Section 8.5) was selected to allow robust data to support a future efficacy study.

10.2 Methods of Analysis

Data will be analysed using a combination of Excel for Mac 2016 (Microsoft Corporation), Prism 5 (GraphPad software) and R. Summary data will be presented as a median and range for all six patients. Categorical data will be presented as raw data.

Patient mortality will be compared to other patients who were managed by LAS on non-study days. These data are stored in a bespoke Cardiac Arrest database, for which London Ambulance Service NHS Trust is the Data Controller. Only patients cared for concurrently with this study will be used for matching. London Ambulance Service NHS Trust will provide these data to the Chief Investigator after the last patient has been enrolled.

Patients will be matched based on their likelihood of receiving ECMO on a one to many basis. Potential matches will be first screened for the study inclusion and exclusion criteria. A priori defined factors that may be used to estimate this likelihood of receiving are:

- age (closest match to 5 years)
- time of first LAS resource attendance on scene (closest match to 5 minutes)
- presumption of a cardiac aetiology to the arrest

Three techniques will be used in matching – individual matching, propensity score matching and GenMatch matching. Matching will be undertaken with replacement. Missing data will not be imputed.

11. Ethical and regulatory considerations

11.1 Protocol

This protocol was constructed in line with the SPIRIT 2013 recommendations [22]. Approval of the protocol was granted by the Trial Steering Committee.

11.2 Peer review

Independent expert peer reviews of this protocol were sought from:

- The Barts Heart Centre Peer Review Committee
- The international ECMO Network (ECMONet)

11.3 Management of actual and potential conflicts of interest

The guidelines of the International Committee of Medical Journal Editors will be used for disclosures of any conflicts of interest (financial and non-financial). Each investigator and member of TSC or DSMC must disclose any conflicts of interest prior to commencing the study. These data will be included in the Trial Master File and be renewed every six months. Any reported conflict will be discussed with the Sponsor and Funders.

11.4 Summary of main ethical, legal and management issues

The main ethical considerations are:

- Emergency enrolment of patients who lack the capacity to provide consent
  Patients are unable to provide consent to enter the study at the point of enrolment as they lack capacity since they are unconscious and in cardiac arrest. This situation is sudden and unexpected preventing prior consultation with the patient and prospective consent. Their capacity will not vary throughout the intervention period as they will remain in cardiac arrest

and unconscious. Since there are no alternative groups of patients in whom this study could be conducted it is necessary to recruit patients who lack capacity.

If it were possible to find a personal consultee for the patient, it is unlikely that the consultee could make an informed decision about the study in the limited time available and in the context of the distress of learning the patient is in cardiac arrest.

Since even short delays in resuscitation and emergency treatments are associated with worse patient outcomes, there is insufficient time to find and contact a professional consultee such as the patient's general practitioner.

Finally, it is considered that since the intervention is likely to benefit the patient directly and that this is proportional to the burden of taking part; particularly in the context that they are in cardiac arrest and have a rate of survival of less than 10% without any additional intervention.

If established, ECMO support will be life-sustaining. Therefore a personal consultee will not be asked if the participant should remain in the study. Nevertheless, they will be consulted about the patient's other medical conditions and likely wishes and these will be considered, according to standard clinical practice, by the attending physicians who will not be study investigators. Family and friends of study participants will be given information about the study as soon as is practicable in the form of face to face discussions and information leaflets.

Participants will be approached if they regain capacity to inform them of their participation in the study. This will be done prior to hospital discharge and usually be on the hospital ward when they are no longer critically unwell. Individual patients can ask to be withdrawn from the study if they request to do so. The patient will not be required to provide a reason for wanting to withdraw from the study. Withdrawal from the study will not influence the goals of on-going medical care for that patient.

If patients never regain capacity due to death or severe neurological injury then they will never be an opportunity to ask them about their inclusion in the study. We will retain and process any data collected about the patient within the constraints outlined the General Data Protection Regulation. We will retain some of the excess plasma and serum collected as part of routine clinical measurements during the clinical care of the patient.

- <u>Are the results generalisable to other geographical areas?</u>
  This feasibility trial involves a collaboration between Barts Health, London Ambulance Service and London's Air Ambulance. These are three well-resourced institutions who have established the logistics to deliver very rapid emergency pre-hospital care in London. If the study demonstrates it is feasible to deliver ECPR within 30 minutes in London, is this generalisable to other urban and non-urban areas?

  A key aspect of this study design is testing the training and simulation that has developed the new ECMO team and these will translate to other geographic areas. It is very likely that other urban centres will be able to replicate the service. We have been approached by other centres keen to participate in a multicentre outcome study if feasibility is demonstrated.

  By contrast, it may take longer for an ECMO team to attend patients in non-urban settings due to the distances that need to be covered but in part mitigated by reduced traffic. Whilst a 30 minute threshold may not be possible in these settings although the processes and lessons learnt may enable accelerated ECPR in these settings too. This parallels the different provision in rural areas for other service such as major trauma centre access or emergency primary coronary intervention access.

- <u>ECPR may increase survival but with neurological injury</u>
  If ECPR restores blood flow to the patients' vital organs such as the heart, liver, brain, kidneys and gut it is possible that this is sufficient to enable the patient to survive but insufficient to prevent brain injury. However, observational data from patients who receive

ECPR suggest that the proportion of surviving patients without severe neurological injury improves. Nevertheless this question will be a core question of any outcome study if the current study demonstrates the feasibility of the intervention.

- Maintenance of patient dignity and privacy in the pre-hospital setting
  We specifically asked at a public engagement event about patient dignity and the impact of a procedure which required insertion of plastic tubes into the groin and exposure of the patient's lower abdomen, pelvis and upper thighs. The universal opinion was that this was unavoidable and outweighed by the potential benefits of the intervention. We will endeavour to maintain patient dignity by utilising windowed drapes that will cover a patient again apart from a small region in the upper thigh. Moreover, the paramedics and pre-hospital physicians in this study are well versed in scene control and will manage bystanders appropriately. They are often assisted in this by the simultaneous attendance of the police in public areas.

- ECPR may impede standard ALS algorithms
  Institution of ECPR could impede standard ALS algorithms as pipes are inserted into the femoral vessels. Our protocol does not involve any interruption of conventional resuscitation which will continue for at least 20 minutes – the time period when a return of spontaneous circulation (ROSC) is most likely and a scenario that is best for the patient. Following 20 minutes the number of patients who go on to survive without disability are few and proportionally reducing rapidly. By contrast the number of patients who go on to die or who have severe disability are many and increasing rapidly. This justifies the addition of an alternative resuscitation strategy to augment the continued standard resuscitation algorithms. Most ambulance services in England follow the European Resuscitation Council guidelines for pre-hospital resuscitation, which advise at least 20 minutes of CPR for all attempted resuscitations. If there is failure to achieve ROSC and the cardiac rhythm is asystole, then the resuscitation is terminated typically. Resuscitation may also be stopped if the cardiac rhythm is pulseless electrical activity (PEA) after discussion with a clinical support desk. If the rhythm is refractory ventricular fibrillation/tachycardia, the patient will be transported with on-going CPR to the nearest emergency department or heart attack centre.

- Pre-hospital ECPR may be associated with a higher risk of procedural complications
  Undertaking a complex in-hospital procedure in the pre-hospital environment could potentially increase the risk of complications from the procedure. We have completed a complex risk assessment matrix within our protocol and have introduced measures to reduce all risks. In published reports of pre-hospital ECPR, the complication rates are no more than that of in-hospital ECPR.

  An alternative strategy to institute ECPR earlier is to start moving the patient the hospital to earlier (colloquially called to 'scoop and run'). Since it is not possible to prospectively identify patients who cannot be resuscitated within 20 minutes, this strategy will require all patients to be transport immediately to hospital with chest compression continuing en route. Evidence has demonstrated that CPR is inferior during transport and therefore such a strategy would risk potential early ROSC in patients by delivering sub-optimal resuscitation in a bid to shorten transfer times.

11.5 Research Ethics Committee (REC) review and reports

The Chief Investigator (CI) has obtained approval for this study from the London Harrow NHS Research Ethics Committee. The study will be submitted for Site Specific Assessment at St Bartholomew's Hospital. The Chief Investigator will require a copy of the Site Specific Assessment approval letter before the study can commence.

All substantial amendments that require review by the REC will not be implemented until the REC and Sponsor grant a favourable opinion regarding the amendment.

All correspondence with the REC will be retained in the Trial Master File. It is the Chief Investigator's responsibility to provide an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable will was given, and annually until

the trial is declared ended (Section 7.9) The CI will notify the REC when the trial ends, even if this is early. In the context of early discontinuation, the REC should be informed of the reasons for this. The CI will be responsible for submitting a final report within one year of the end of the study, indicating the results and any publications or abstracts to date.

11.6 Annual Safety Reporting

The CI will send an Annual Progress Report to the REC and the sponsor using the Health Research Agency template on the anniversary of the REC "favourable opinion".

12. Public Involvement

Patients and publics were involved in the design of this study through a Patient and Public Engagement event held at 2 May 2017. Specific questions asked in addition to a general open session centred around:

- concerns about consent and permission to enter a study when patient lacks capacity since they are in cardiac arrest
- concerns about preserving patients' dignity, autonomy, and privacy in the context of resuscitation that is happening outside a healthcare setting
- appropriate outcome measures that may demonstrate benefit or harm
- communication of the study to a wider audience

A lay person will be asked to join the Trial Steering Committee and will contribute to the discussions on the study management and dissemination of findings.

The study will be registered with the INVOLVE open-access database which registers healthcare projects involving members of the public as partners in the research process (http://www.invo.org.uk).

13. Data handling and record keeping

13.1 Data management

Study data will be collected and managed using REDCap electronic data capture tools hosted at Queen Mary University of London. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Each major version of the CRF must be authorised by the Trial Steering Committee. Minor versions correcting typographical errors can be authorised by the Chief Investigator. All versions will be stored in the Trial Master File.

Each patient will be identified by a unique participant identification code. All person identifiable data will be logged on the Study Identification Log which will be part of the Investigator Site File, and used by the study team for participant contact. A study enrolment log will be maintained with pseudo-anonymised participant data.

Signed completed CRFs will be stored along with copies of source data (e.g. ambulance run sheet, medical records, clinical charts, drug charts) in the Investigator Site File which will be maintained in a secure location at St Bartholomew's Hospital. The CRF will be compliant with the CVCTU's Standard Operating Procedure for Trial Data Management. The Trial Master File (TMF) will be maintained by the CVCTU and kept in a secure, restricted access office within the William Harvey Research Institute.

13.2 Source data

All versions of Consent Forms must be the authorised by the Sponsor and REC. All versions will be stored in the Trial Master File.

All original signed consent forms will be stored in the Investigator Site File. Copies will be scanned and inserted in the Cerner Millennium Electronic Health Record of Patients. The consenting procedure will follow the CVCTU's Standard Operating Procedure and the investigator taking consent will be trained in consent procedures and Good Clinical Practice (GCP).

If possible, source data will be collected directly into the REDCap. In the pre-hospital setting this will not be possible and data will be collected onto a paper CRF which will be transferred to the REDCap subsequently. A source data agreement will be written to specify where the source will be located. All source data will be kept securely in the participant study files within locked cabinets in restricted access rooms in St Bartholomew's Hospital.

All times will be recorded in Coordinated Universal time (UTC) to avoid confusion over transitions between British Summer Time and GMT. All times (e.g. medical devices, LAS dispatch desk, research clocks in study equipment, watches) will be assessed for accuracy against the time.is time server.

13.3 Confidentiality

The investigators will preserve the confidentiality of participants taking part in the study in line with General Data Protection and Regulation and Data Protection Act (2018), NHS Caldicott principles, and UK Policy Framework for Health and Social Care. Data access will be granted to authorised representatives from the Sponsor, St Bartholomew's Hospital and any regulatory authority to permit monitoring, audits and inspections.

All paper files will be stored in locked cabinets in restricted access rooms.

Any electronic records of the data created during analysis of the study will not contain person identifiable data and will be stored on a network drive of Barts Health NHS Trust. Access to this area will be granted to the named study investigators.

The LAS provision of the Cardiac arrest database of matched controls (single data transfer) to the Chief Investigator after the end of the study recruitment will only include anonymised data, and data will be transferred between nhs.net emails to ensure data protection and confidentiality. Any missing data will be queried with the host establishment by the LAS team.

13.4 Record Retention and Archiving

The Trial Master File will be stored securely for a minimum of 20 years after the study end (Section 7.9) and in accordance with the CVCTU's Standard Operating Procedure. The Chief Investigator will be responsible for the security of the data but may delegate this to any storage repository, approved by the JRMO.

All electronic copies of data will be deleted two years after publication of the study (Section 8.9).

The UK Policy Framework for Health and Social Care Research requires that research records are kept for 20 years after the project has completed. For studies sponsored by Barts Health NHS Trust the approved repository for long-term storage of local records is the Trust Corporate Records Centre. All research documentation must be archived in physical form – source data collected electronically will be printed and certified as authentic by the investigators. Electronic archiving is not accepted.

14. Laboratories

14.1 Central and local laboratories

The central laboratories for Barts Health NHS Trust will provide haematological, coagulation and biochemical assessments outlined in Table 2. The central and satellite Haematology, Blood Coagulation and Clinical Biochemistry laboratories have Certificates of Accreditation with Clinical Pathology Accreditation (UK) Ltd. The laboratories are also registered with UK National External Quality Assessment Services (UK NEQAS).

14.2 Sample collection, preparation and procedures

Blood samples will be taken as part of routine clinical practice. Therefore they will be requested, sampled, labelled and analysed according to the practices and policies at Barts Health NHS Trust for all clinical samples.

14.3 Sample storage and transfer

Excess serum and plasma are stored by the laboratories routinely for seven days to facilitate additional tests or confirmatory tests. These samples are stored at -20°C in the clinical laboratories. After the usual retention period for the clinical laboratories the excess serum and plasma will be transferred to the study team. Thereafter samples will be stored at -80°C. Samples will be labelled with the study ID and no patient identifiers. The chain of custody will be recorded in the Investigator Site File according to the study Standard Operating Procedures (Table 4). Subsequent analysis of these samples will require appropriate research approvals to be in place. All samples will be destroyed using standard laboratory procedures after 3 years.

15. Interventions and tools

15.1 Devices

The CARDIOHELP-i ECMO device (Maquet, Rastatt, Germany) is a CE marked device with an intended purpose which encompasses this investigation (see Table 6). Therefore, the Medicines and Healthcare products Regulatory Agency does not need to notified about this study.

The CARDIOHELP-i device is classified in accordance with Council Directive 93/42/EEC concerning medical products, Appendix IX as a Class IIb device. It is defibrillator-protected Type CF in accordance with IEC 60601-1.

All devices will be submitted to Clinical/Medical Physics, Barts Health NHS Trust, for assessment according to the Trust policy on the management of medical equipment (CLI/POL/151/2014-001 or any superseding version).

The device will be used with an HLS Set Advanced 7.0 disposable. This is delivered sterile and pyrogen-free. It is stored in a cool, dark and dry place between 10-30 °C.

Table 6 Intended purposes of the CARDIOHELP-i (Maquet)

Purpose	Description
Intended use	To drive, control, monitor and record an extracorporeal circulation For intra-hospital and inter-hospital patient transportation and for continuous operation
Intended user	Trained specialist medical staff
Intended patients	All patients independent of age, size and weight
Intended environments	Operating rooms, catheter laboratories, emergency departments and intensive care units In addition, the CARDIOHELP System can be used for intra-hospital and inter-hospital patient transportation in vehicles such as ambulances and aircraft as well as for emergency use outside a clinical environment

Taken from the Instructions for Use, Revision 1.5, Issued October 2014

15.2 Techniques and interventions

The suggested specific techniques for pre-hospital ECMO are outlined in the latest version of the Study Manual. This details:

- Team composition
- Daily checks and team preparedness
- Dispatch of the ECMO team
- Initial patient assessment
- Priming of the ECMO circuit
- Insertion of guidewires into the femoral vessels
- 20 minute time out procedure

- Cannulation of the femoral vessels and commencement of ECMO
- Post ECMO/ROSC care including transfer to the Heart Attack Centre
- Care at the Heart Attack Centre

15.3 Tools

15.3.1 EQ-5D-5L

The EQ-5D-5L questionnaire will be used to assess quality of life in patients at 3 months [23]. This is a validated questionnaire and a license to deliver this questionnaire has been granted. Instructions for the use of this instrument are outlined in a trial Standard Operating Procedure (Table 4) to minimise inter-observer variations. We may administer the questionnaire using the usual ICU video-conference clinic, which has been established following the COVID-19 pandemic to reduce the need for vulnerable patients to travel to the hospital.

15.3.2 Modified Rankin Scale of neurological assessment

The modified Rankin Scale will be used to assess neurological disability in patients at hospital discharge and 3 months [24]. Instructions for the use of this instrument are outlined in a trial Standard Operating Procedure (Table 4) to minimise inter-observer variations. We may administer the questionnaire using the usual ICU video-conference clinic, which has been established following the COVID-19 pandemic to reduce the need for vulnerable patients to travel to the hospital.

15.3.3 Functional independence measure

The Functional Independence Measure is an internationally validate tool that will provide a detailed assessment of patients' functional status over the domains of self-care, sphincter control, transfers, locomotion, communication and social cognition [25]. Assessors will have undergone specific training in the use of the instrument and will follow the trial Standard Operating Procedure for its use (Table 4) to minimise inter-observer variations. We may administer the questionnaire using the usual ICU video-conference clinic, which has been established following the COVID-19 pandemic to reduce the need for vulnerable patients to travel to the hospital.

15.4 Non-investigational medicinal products (NIMPs)

The non-investigation medicinal products used in the study are outlined in Table 7. Many other drugs may be used in the care of the patient as dictated by the attending clinicians.

Table 7 Non-investigational medicinal products

Medicinal product	Comments	Storage requirements
Oxygen/Medical air mixture	Sweep gas for ECMO circuit	Keep away from extremes of heat
Rocuronium bromide	As neuromuscular blockade	2-8°C
Teicoplanin	As antibiotic prophylaxis for surgical site infection	None
Heparin sodium	As an anticoagulant for ECMO	Below 25°C
Compound sodium lactate	For priming of the ECMO circuit	None

The pre-mixed oxygen/medical air mixture will be prepared as a special gas by the British Oxygen Company. It will be stored in accordance with the Health Technical Memorandum 02-01: Medical gas pipeline systems (Part B Operational management) produced by the Department of Health and outlined in the trial Standard Operating Procedure for the Management of medical gases. Specifically, a suitable storage area (BNB_06_071 in King George V Building, St Bartholomew's Hospital) has been approved by the trial pharmacist. A chain of custody will be maintained for all non-investigation medicinal products. A Summary of Product Characteristics (SPC) for each NIMP will be stored in the Trial Master File. The Undesired Effects outlined in these SPC will act as Reference Safety Information to enable attribution of causality and expectedness when classifying adverse events (Section 16.3).

16. Safety reporting

16.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

16.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

16.3 Classification of Adverse Events and Reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

All Serious Adverse Events will be assessed for causality and expectedness, using the definitions in Table 8 and Table 9. Reference Safety Information for this assessment is included in Table 9 and Summary of Product Characteristics for the NIMPS outlined in Table 7.

Table 8 Definitions of relationship of an SAE to study intervention

Relationship		Definition
Unrelated		There is no evidence of any causal relationship
Related,	Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
	Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
	Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
	Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable		There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Table 9 Definitions of expectedness of an SAE for the study intervention

Expectedness	Definition
Unexpected	Unexpected events are those not anticipated but could relate to the study. Events that are of a more serious form that would be expected should also be considered as unexpected.

Expected	Expected events are: -Failure to cannulate a patient for ECMO -Hypoxic brain injury -Death due to myocardial failure -Death due to hypoxic brain injury -Vascular damage during cannulation in adverse environment -Bleeding at site of cannulation -Infection at site of cannulation -Intracranial haemorrhage -Gastrointestinal haemorrhage -Events outlined in the Undesired Effects section of the SPC for each NIMP

16.4 Notification and reporting of Adverse Events and Reactions

If the AE is not defined as serious (see Section 16.3), the AE will be recorded in the study documents, and the participant followed up by the research team. The AE will be documented in the participants' source documents, the electronic Case Report Form (CRF) in REDCap, and, where appropriate, medical records.

Medical judgement will be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

16.5 Notification and reporting of Serious Adverse Events

SAEs will be reported to the REC where in the opinion of the Chief Investigator the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in Table 9).

All SAEs will be reported to the CVCTU within 24 hours of site notification via the REDCap SAE eCRF, and will be recorded in the study SAE log and will constitute part of the routine statutory safety reporting to the Research Ethics Committee (REC). Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe. Any additional relevant information must be reported within 8 days of sending the first report.

16.6 Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However, the CI will inform the sponsor and Research Ethics Committee (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

16.7 Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

16.8 Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

The CVCTU will have oversight of safety reporting, and will monitor the study to ensure all SAEs are identified and reported in the required timelines to the Sponsor and REC as required.

17. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

The CVCTU will monitor the study, with reference to both the CVCTU's Standard Operating Procedure and following the study specific monitoring plan. Monitoring will be conducted to ensure data integrity and patient safety, as well as compliance to the protocol and GCP. Both on-site visits and central monitoring of data via the REDCap database will be performed. Monitoring reports will be written and made available to the Sponsor. Monitoring will include source data verification, query resolution and review of GCP and protocol compliance. Protocol deviations will be logged in the Trial Master File and be reported to the Chief Investigator and Sponsor. Frequently recurring breaches are not acceptable and will require immediate action to prevent the variations.

The Joint Research Management Office (JRMO) of Barts Health NHS Trust may audit the study to determine whether the trial related activities were conducted, and that data were recorded, analysed and accurately reported according to the protocol, CVCTU's Standard Operating Procedures and Good Clinical Practice (GCP). Audits will be triggered:

- if the JMRO's identifies a need during the risk assessment process.
- following an allegation of research misconduct or fraud or a suspected breach of regulations
- at random

18. Trial committee and investigator arrangements

18.1 Trial steering committee (TSC)

A Trial Steering Committee will be constituted and will be chaired by an independent expert. It will be set up and run according to the principles outlined in the CVCTUs Standard Operating Procedure. Terms of reference (TOR) for committees will be agreed before the commencement of the trial. All members of committees must agree and sign the TOR before recruitment into the trial begins. Meetings will be formally minuted with actions recorded and stored in the Trial Master File.

The TSC will provide oversight to the conduct of the study on behalf of the study Sponsor and Funder.

The TSC will meet at least after the first two patients are recruited or at least every 6 months either face to face or by teleconference. Meetings will be scheduled in parallel with the DSMC meetings, typically following the DSMC. Observers from the Sponsor and Funder will be invited and may be in attendance.

18.2 Data Safety and Monitoring Committee (DSMC)

A Data Monitoring and Safety Committee will be constituted that will be chaired by an independent expert. It will be set up and run according to the principles outlined in the CVCTU's Standard Operating Procedure. Terms of reference (TOR) for committees will be agreed before the commencement of the trial. All members of committees must agree and sign the TOR before recruitment into the trial begins.

The DSMC will be responsible for:

- monitoring any trial data
- making recommendations to the TSC on whether there are any ethical or safety reasons why the study should not continue
- advising the TSC regarding the release of data and/or information
- consider data emerging from other studies.

The DSMC will meet after the first two patients are recruited or at least every 6 months either face to face or by teleconference. Additional meetings may be convened at the request of the DSMC

or if there are any safety concerns. Observers from the Sponsor and Funders will be invited and may be in attendance.

18.3 Investigators

The investigators are responsible for ensuring that the study is conducted according to this protocol and any applicable regulations.

All investigators will have undergone a training program that aims to provide each investigator with a thorough working knowledge of the protocol, study manual, associated standard operating procedures and applicable regulations and competence to perform their specific roles. The specific requirements are outlined in the latest version of the Study Training Manual.

All investigators will have undergone Good Clinical Practice training in the previous two years and will renew this appropriately.

The Chief Investigator will ensure that the study records are complete, accurate and current. These records will include the following materials:

- Correspondence with the Sponsor, the Trial Steering Committee, the investigators, the funders and the Research Ethics Committee (REC).
- Accountability of records of receipt, use, and disposition of all investigational devices and study materials, including the type and quantity, date of receipt, any serial/batch number and the names of all persons receiving, using and disposing of such items
- Study Subject Records, including Informed Consent forms, copies of all completed Subject Case Report Forms (CRFs) and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.).
- All relevant observations, including records concerning adverse events (whether anticipated or unanticipated)
- Current study protocol and protocol deviation log, with dates and details of any reason for deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects
- The approved blank Informed Consent form and blank Subject CRFs
- Certification that the Protocol has been approved by all of the necessary approving authorities
- Signed Investigator's Agreements with curricula vitae of all participating Investigators

The Chief Investigator will be responsible for the following reports:

- Serious adverse events
- Deviations from the investigational plan
- Annual progress reports to the study Sponsor, Funders and REC.
- Final report to the study Sponsor, Funders and REC. The end of study declaration will be made to the REC within 90 days of the end of the study, and the end of study report will be submitted within 1 year of the end of study. This will be produced irrespective of whether the study finishes as scheduled or is terminated early.

19. Finance and funding

This study is funded by:

- London’s Air Ambulance Charity through an unrestricted research grant
- Barts Charity through an unrestricted research grant
- Maquet Cardiopulmonary GmbH through unrestricted funding that provides free ECMO disposables to the study.

20. Indemnity

The NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

21. Dissemination of research findings

A manuscript summarising the study will be drafted by the chief investigator following completion of the study. It will be formulated according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Template for Intervention Description and Replication (TIDieR) checklist and guide [26, 27] The chief investigator will be responsible for the integrity of the data contained within the manuscript and accuracy of the analysis. All investigators will have full access to the data and provide interpretation and critical revision of the manuscript. Any funders will have no role in the preparation, review or approval of the manuscript.

Authorship credit will be according to internationally agreed guidelines (www.icmje.org) that require authors to fulfil all of the following criteria:

- substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content

An electronic version of published research papers will be made freely available in Europe PubMed Central as soon as possible and definitely within 6 months of publication. We will share an electronic version of the manuscript with patients who participated in the study and any patients and publics involved in the study design and conduct.

Any results communicated via the press, social media or internet will be done following consultation and agreement of the press officers of Barts Health NHS Trust and the funders.

All research participants will be informed of the results via letter with 6 months of the study ending.

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