Statistical Analysis Plan

Study 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.
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Signature Page

I give my approval for the Statistical Analysis Plan (Version 1.0, 10 April 2019) for the study titled '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'.

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Contents

1 Glossary of Terms and Abbreviations

AE	Adverse event
CPR	Cardiopulmonary Resuscitation
CVA	Cerebrovascular Accident
DSMC	Data Safety Monitoring Committee
ECMO	Extra-Corporeal Membrane Oxygenation
ECPR	Extracorporeal Cardiopulmonary Resuscitation
EQ-5D-5L	EuroQol Quality of Life questionnaire
FIM	Functional Independence Measure
IHD	Ischaemic Heart Disease
OHCA	Out-of-hospital Cardiac Arrest
MRS	Modified Rankin Scale
PVD	Peripheral Vascular Disease
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.
ROSC	Return of spontaneous circulation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
VA-ECMO	Veno-arterial-ECMO

2 Introduction

This Statistical analysis plan (SAP) has been written based on information from the study protocol version 2.0, dated 29 October 2018.

2.1 Preface

Survival from out of hospital cardiac arrest (OHCA) remains low despite advances in resuscitation science. Within London the London Ambulance Service (LAS) attended 10,116 OHCA in 2015/2016 and attempted resuscitation in 4389. Overall mortality was 91% for those in whom resuscitation was attempted, and even among the subset most likely to survive ("Utstein comparator group" – bystander witnessed cardiac arrests with a shockable rhythm), 35.5% of patients failed to achieve return of spontaneous circulation (ROSC) and the overall mortality was 68.5%. The mortality for those patients with witnessed cardiac arrests but in a non-shockable rhythm was 97.5% (3,353/3,440).

Hospital based extra-corporeal cardiopulmonary resuscitation (ECPR) uses an established technology (VA-ECMO), which provides greater blood flow and oxygen delivery during cardiac arrest than external cardiac massage [1]. The use of ECPR for in hospital cardiac arrest is associated with a stepwise improvement in survival to hospital discharge [2]. In-hospital ECPR is currently considered as a rescue therapy for selected patients [3]. There is no national protocol for its use and it has not been performed in a pre-hospital setting in the UK, nor investigated in a randomised controlled trial.

2.2 Purpose of the analyses

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. If pre-hospital ECMO flow or ROSC 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.

3 Study Objectives and Design

3.1 Design

The study is a single centre feasibility study of a complex intervention. The study aims to recruit six intervention patients. The study will only be performed between 8.00 am and 5.00pm on study days when the ECMO team is available. It is anticipated that this will be 2-3 days per week. Patients will be matched to other patients managed by LAS on non-study days, based on their suitability for ECPR in order to compare mortality between study and non-study days.

3.2 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

3.3 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

3.4 Primary Endpoint

The primary endpoint will be the number and proportion of patients with ROSC or ECMO flow (>50% target) within 30 minutes of the initiation of chest compressions.

3.5 Secondary Endpoints

The following secondary endpoint will be measured:

- number of patients not dispatched to as travel time too great/team unavailable
- the 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 (Yes/No).
- survival to hospital discharge (Yes/No).
- neurological outcome at hospital discharge (modified Rankin scales)
- incidence of ECPR-related complications (failure to cannulate, vascular injury, site infection and distal leg ischaemia) obtained from AE/SAE data.

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
- Inpatient rehabilitation following acute hospital stay (yes/no) and duration.

3.6 Assessment of objectives

The time of ROSC or ECMO blood flow >50% target will be recorded on the CRF. Many assessments will be made as part of routine clinical practice and those below will be recorded on the CRF (Table 1). 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 (Table 2)

Table 1 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 lactate
[e] Including adrenaline, noradrenaline, dobutamine, dopamine, milrinone, levosimendan
[f] Including prothrombin time, activated partial thromboplastin time, fibrinogen, platelet count

Table 2 Non-routine assessments made during the study

Assessment	Pre-ECMO	Time of hospital admission				Hospital discharge	3 month
		0 h	24 h	48 h	72 h		
Bilateral pupillometry	✓	✓	✓	✓	✓		
Serum Neuron Specific Enolase		✓	✓	✓	✓		
Plasma/Serum biobanked [a]	✓	✓	✓	✓	✓		
Modified Rankin Scale						✓	✓
Function Independence Measure						✓	✓
EQ-5D							✓

[a] Biomarkers measured will be Troponin I, BNP, CKMB, NSE and SB100.

3.6.1 Assessment of primary endpoint

The time to cannulation will be calculated as the time from collapse to the ECMO start time and from this the number of patients cannulated within 30 minutes will be obtained.

3.6.2 Assessment of secondary endpoints

Secondary endpoints are described in section 7.5.

Clinical assessment data to be collected is described in section 7.6 along with details of the time points for each endpoint.

Use of the EQ-5D-5L, modified Rankin scale and Functional Independence Measure will be outlined in a trial Standard Operating Procedure.

FIM will be assessed over the domains of self-care, sphincter control, transfers, locomotion, communication and social cognition, as well as motor and cognitive subtotal scores and total FIM score [4]. EQ-5D-5L will be described for 5 dimensions, as well as the visual analogue scale. In addition, a single index value will be calculated (www.euroqol.org).

3.7 Level of significance

The study is descriptive and no hypothesis tests will be conducted.

3.8 Sample size

No power calculation has been undertaken. The study aims to recruit six patients. The sample size has been selected to allow robust data to support a future efficacy study.

4 General Analysis Definitions

4.1 Study period and visit definitions

4.1.1 Visits

On arrival at the scene the ECPR team will assess inclusion/exclusion criteria. If the appropriate criteria are met:

The pre-hospital ECPR team will support the LAS in endeavouring to achieve ROSC.

The ECMO consultants will insert guidewires into femoral vessels and prepare CardioHelp.

If ROSC is achieved within 20 minutes of starting resuscitation, the team will support LAS with standard post-resuscitation care and transfer of the patient to the nearest Heart Attack Centre.

If ROSC is not achieved within 20 minutes the exclusion criteria will be reassessed and if no exclusion criteria are identified the ECMO consultants will proceed to cannulate the patient's femoral artery and vein and commence ECMO support. If cannulation cannot be achieved within 60 minutes then further attempts will not be continued and the patient will be reviewed with consideration to declaring life extinct or transporting the patient under ongoing CPR to the nearest emergency department.

FIM and modified Rankin scale will be assessed at hospital discharge and at 3 months, and EQ-5D-5L at 3 months.

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

4.1.2 Study Scheme Diagram

A flow diagram of study procedures is given in the protocol (section 8.10).

4.1.3 Study Populations

The following populations will be studied:

- All calls which ECPR team dispatched were to
- Patients meeting eligibility criteria on team arrival
- ECPR candidates at 20 minute time-out
- Treated population-Cannulated patients
- Matched controls- controls selected from non-study days, meeting inclusion criteria and individually matched to patients from the treated population.
- Safety population will be the same as the treated population.

Endpoints that will be analysed are outlined in Table 3.

Table 3 Endpoints analysed is specific study populations

Population	Endpoints
Patients with ECPR team despatched	• Time interval between call to the emergency services and ECPR team arrival.
Patients meeting eligibility criteria on team arrival	• Proportion of potentially supportable patients in whom guidewire placement is attempted

	• The number of patients in whom it is attempted to start inserting guidewires but do not meet study inclusion criteria at 20 minute time out. • Proportion of patients who achieve ROSC prior to the 20 minutes timeout.
ECPR candidates at 20 minute time-out	• The number of patients in whom ROSC is achieved prior to ECMO flow. • The number of patients successfully cannulated within 30, 45 and 60 minutes.
Cannulated patients (N=6)	• ECPR-related complications • Organ dysfunction. • Neurological outcome • Survival • Pupillometry • Biomarkers • EQ5D • FIM • MRS
Matched controls	• Survival

4.1.4 Subgroup definitions

Not applicable.

5 Patient Disposition

Participants will be patients with a visible age between 18 and 65 who have a witnessed out-of-hospital cardiac arrest with presumed cardiac aetiology, receive bystander chest compressions within 3 minutes and remain in cardiac arrest or fail to sustain ROSC at 20 minutes. Exclusion criteria are detailed in the protocol section 6.2. Numbers enrolled, withdrawing and completing discharge and 3 month follow-up will be reported.

5.1 Compliance to study drug

Not applicable.

5.2 Exposure to study drug

Not applicable.

6 Demographics and Baseline characteristics

Age, gender, ethnicity and time of LAS attendance on scene will be described for intervention patients and matched controls. In addition, we will describe the following risk factors – diabetes, PVD, IHD, CVA, smoking, frailty index.

7 Interim analysis and timing for analysis.

7.1 Interim analysis

No formal interim analysis is planned. A Data Safety Monitoring Committee (DSMC) will be set up and will be responsible for monitoring trial data and making recommendations on whether it is ethical and safe to continue the study. Recruitment, safety and demographic

information of participants will be reported to the DSMC. Additional analysis may be undertaken if requested by the DSMC.

7.2 Time points for analysis.

The DSMC will meet at least every three months. All other analysis will take place at the end of the study.

8 Efficacy Analysis

8.1 Method for analysis of endpoints

8.1.1 Analysis of primary endpoint

Analysis will be descriptive. Results will be presented as the total number, and the number and proportion of patients with ROSC or ECMO flow (>50% target) in the treated population.

8.1.2 Analysis of secondary endpoints

Analysis will be descriptive.

Categorical variables will be presented as the number and proportion of patients with the endpoint in the treated population. For the survival endpoint numbers and proportions will be presented for both treated and control patients.

Continuous variables will be presented as the median and range for the intervention patients.

8.1.3 Analysis of subgroups

Not applicable

8.1.4 Covariate adjusted analysis

Not applicable

8.1.5 Matching of controls to patients

Potential controls will be screened for inclusion and exclusion criteria including a cardiac aetiology. Only patients cared for concurrently with the study will be used. Controls will be individually matched to up to 5 patients, using age (within 5 years) and time of LAS attendance on scene (within 5 minutes). Matching with relacement will be performed but also matching without replacement in a planned sensitivity analysis.

8.2 Assumptions for analysis.

The analysis is descriptive and makes no assumptions about the data.

8.3 Methods for handling of missing data and outliers

All available data will be used for each endpoint. Due to the small number of patients and the descriptive nature of the analysis, data will not be imputed.

8.4 Multiple comparisons

Not applicable

8.5 Multiple-centre studies

Not applicable

9 Safety analysis

The number of subjects having at least one AE will be presented. The number of subjects with AEs of mild/moderate/severe intensity will be shown as well as the total number of AEs allowing multiple events per patient.

SAEs will be listed along with details including whether the event is unexpected and whether it is thought to be related to the treatment.

10 References

1. Virdi, G., S. Picton, and R. Fothergill *London Ambulance Service NHS Trust Cardiac Arrest Annual Report: 2014/15*. 2015.

2. Fagnoul, D., A. Combes, and D. De Backer, *Extracorporeal cardiopulmonary resuscitation.* Curr Opin Crit Care, 2014. 20(3): p. 259-65.

3. Soar, J., et al., *Adult advanced life support guidelines*. 2015.

4. Keith, R.A., et al., *The functional independence measure: a new tool for rehabilitation.* Adv Clin Rehabil, 1987. 1: p. 6-18.

11 Document history and version control

All versions will be dated and numbered in the format N.x, where N is a numeric value that is increased when a major change is made. The postscript x relates to minor changes typically for typographical errors that do not substantially alter the conduct of the tool.

The full history is outlined in Table 4.

Table 4 Version history

Version	Date	Notes
1.0	10 April 2019	First authorised version of Statistical Analysis Plan