



## PROTOCOL

### PROTECTeD: Exploring and Improving Resuscitation Decisions in Out of Hospital Cardiac Arrest

PROSPERO Number: CRD42019131010  
Sponsor: University of Warwick & University Hospitals Birmingham NHS Foundation Trust  
Funding Body: NIHR Health Services Delivery Research  
IRAS Number: 264842  
Ethics Approval date: East Midlands – Derby Research Ethics Committee, 23 March 2020

Version Number: 3.0  
Date: 05 October 2021  
Stage: Draft

Protocol Amendments				
Amendment No.		Date of Amendment		Date of Approval
1		13 October 2021		TBC

## CONTACT NAMES AND NUMBERS

Role	Name, address, telephone
<b>Sponsor:</b>	<p>Ms Carole Harris University of Warwick Gibbet Hill Road Coventry Tel: 02476 522746 Email: <a href="mailto:c.d.harris@warwick.ac.uk">c.d.harris@warwick.ac.uk</a></p> <p>Clark Crawford Head of Research Governance University Hospitals Birmingham NHS Foundation Trust Tel: 0121 371 4186 Email: <a href="mailto:R&amp;D@uhb.nhs.uk">R&amp;D@uhb.nhs.uk</a></p>

Role	Name, address, telephone
<b>Chief Investigators:</b>	<p>Prof Gavin Perkins  Director Warwick Clinical Trials Unit,  University of Warwick  Tel: 02476 150479  Email: <a href="mailto:g.d.perkins@warwick.ac.uk">g.d.perkins@warwick.ac.uk</a></p> <p>Dr Mike Smyth  Assistant Professor of Emergency and Critical Care,  Warwick Clinical Trials Unit, University of Warwick  Tel: 02476 528039  Email: <a href="mailto:m.a.smyth@warwick.ac.uk">m.a.smyth@warwick.ac.uk</a></p>
<b>Study Manager:</b>	<p>Mrs Lauren Betteley  Clinical Trials Manager,  Warwick Clinical Trials Unit, University of Warwick  Tel: 02476 575849 / 523709  Email: <a href="mailto:lauren.betteley@warwick.ac.uk">lauren.betteley@warwick.ac.uk</a>  <a href="mailto:protected@warwick.ac.uk">protected@warwick.ac.uk</a></p>
<b>Senior Project Manager</b>	<p>TBC  Senior Project Manager  Warwick Clinical Trials Unit, University of Warwick  Tel: TBC  Email: <a href="mailto:protected@warwick.ac.uk">protected@warwick.ac.uk</a></p>

<b>Co-investigators:</b>	<p> Prof Frances Griffiths  Professor of Social Sciences,  University of Warwick  Tel: 02476 174270  Email: <a href="mailto:f.e.griffiths@warwick.ac.uk">f.e.griffiths@warwick.ac.uk</a> </p> <p> Prof Anne-Marie Slowther  Professor of Clinical Ethics,  University of Warwick  Tel: 02476 174513  Email: <a href="mailto:a-m.slowther@warwick.ac.uk">a-m.slowther@warwick.ac.uk</a> </p> <p> Prof Ranjit Lall  Professor of Clinical Trials,  Warwick Clinical Trials Unit, University of Warwick  Tel: 02476 174649  Email: <a href="mailto:r.lall@warwick.ac.uk">r.lall@warwick.ac.uk</a> </p> <p> Prof Aloysius Niroshan Siriwardena,  Professor of Primary and Prehospital Healthcare  Health and Social Care,  University of Lincoln  Tel: 01522 886939  Email: <a href="mailto:nsiriwardena@lincoln.ac.uk">nsiriwardena@lincoln.ac.uk</a> </p> <p> Prof Rachael Fothergill  Head of Clinical Audit &amp; Research,  London Ambulance Service  Tel: 02077 832504  Email: <a href="mailto:rachael.fothergill1@nhs.net">rachael.fothergill1@nhs.net</a> </p> <p> Dr Terry Brown  Research Fellow,  Warwick Clinical Trials Unit, University of Warwick  Tel: 02476 174624  Email: <a href="mailto:t.brown.1@warwick.ac.uk">t.brown.1@warwick.ac.uk</a> </p>
--------------------------	---

Role	Name, address, telephone
	<p>Mr John Long Patient Public Involvement Email: <a href="mailto:johnpatlong@aol.com">johnpatlong@aol.com</a></p> <p>Prof Aileen Clarke Professor of Public Health and Health Services Research, University of Warwick Tel: 02476 150189 Email: <a href="mailto:aileen.clarke@warwick.ac.uk">aileen.clarke@warwick.ac.uk</a></p> <p>Prof Stavros Petrou Professor of Health Economics, Department of Primary Care Health Sciences, University of Oxford Tel: 01865 589506 Email: <a href="mailto:Stavros.petrou@phc.ox.ac.uk">Stavros.petrou@phc.ox.ac.uk</a></p>
<b>Statistician:</b>	<p>Felix Michelet Research Associate Warwick Clinical Trials Unit, University of Warwick Tel: 02476 522207 Email: <a href="mailto:felix.michelet@warwick.ac.uk">felix.michelet@warwick.ac.uk</a></p>
<b>Senior Research Fellow:</b>	<p>Dr Bronwyn Harris Senior Research Fellow Warwick Clinical Trials Unit, University of Warwick Tel: 02476 575859 Email: <a href="mailto:b.harris.2@warwick.ac.uk">b.harris.2@warwick.ac.uk</a></p>
<b>Health Economist:</b>	<p>Kamran Khan Research Fellow Warwick Clinical Trials Unit, University of Warwick Tel: 02476 574642 Email: <a href="mailto:k.a.khan@warwick.ac.uk">k.a.khan@warwick.ac.uk</a></p>
<b>Patient and Public involvement co-ordinator:</b>	<p>Ms Teresa Melody Chair of Patient and Public Research Advisory Group (CRAG) University Hospitals Birmingham NHS Foundation Trust Tel: 0121 424 3732 Email: <a href="mailto:teresa.melody@heartofengland.nhs.uk">teresa.melody@heartofengland.nhs.uk</a></p>

Role	Name, address, telephone
<b>Expert Advisory Group:</b>	<p>Ms Catherine James (AACE guidelines)</p> <p>Dr Dhushy Surendra Kumar (JRCALC)</p> <p>Dr Julian Mark (NASMed, AACE)</p> <p>Prof Tom Quinn (RCN)</p> <p>Dr Caroline Leech (RCEM, FPHC RCS Ed)</p> <p>Prof Charles Deakin (RCUK, RCoA)</p> <p>Mr Mark Whitbread (Ambulance Service Cardiac Leads group)</p> <p>Mr Paul Gowans (College of Paramedics)</p> <p>Jo Stonehouse (College of Paramedics End of Life Care Lead)</p> <p>Mr John Long (PPI)</p>
<b>Study Steering Committee:</b>	<p>Chair: Prof Alison Richardson</p> <p>Professor in Cancer Nursing and End of Life</p> <p>University of Southampton</p> <p>Health Sciences Building, 67 Highfield Road, Southampton</p> <p>SO17 1BJ</p> <p>Tel: 02380 798494</p> <p>Email: <a href="mailto:alison.richardson@soton.ac.uk">alison.richardson@soton.ac.uk</a></p> <p>Dr John Black</p> <p>Medical Director</p> <p>South Central Ambulance Service NHS Foundation Trust</p> <p>Email: <a href="mailto:John.Black@scas.nhs.uk">John.Black@scas.nhs.uk</a></p> <p>Prof Julia Williams</p> <p>Professor of Paramedic Science</p> <p>University of Hertfordshire</p> <p>School of Health and Social Work, Hatfield, Hertfordshire</p> <p>AL10 9AB</p> <p>Email: <a href="mailto:j.williams@herts.ac.uk">j.williams@herts.ac.uk</a></p> <p>Ms Deirdre Folan</p> <p>Lay Representative</p>

Role	Name, address, telephone
	<p>For general queries and supply of study materials please contact the coordinating centre:</p> <p>PROTECTeD Study Office</p> <p>Warwick Clinical Trials Unit (WCTU)</p> <p>The University of Warwick</p> <p>Gibbet Hill Road</p> <p>Coventry</p> <p>CV4 7AL</p> <p>Tel: 024 7652 3709</p>

## TABLE OF CONTENTS

	TABLE OF CONTENTS .....	8
	LAY SUMMARY .....	11
	STUDY SUMMARY.....	12
	LIST OF ABBREVIATIONS/GLOSSARY .....	13
1.	BACKGROUND .....	15
1.1	Epidemiology and burden of the condition .....	15
1.2	Existing knowledge .....	15
1.3	Research Question .....	18
1.4	Need for a study .....	18
1.5	Ethical considerations .....	20
2.	STUDY DESIGN .....	22
2.1	Study summary and flow diagram .....	22
2.2	Aims and objectives.....	24
2.2.1	Primary objective .....	24
2.2.2	Secondary objective .....	24
2.3	Recruitment Summary .....	24
2.4	Eligibility criteria .....	24
2.4.1	Exclusion criteria .....	24
3.	SYSTEMATIC REVIEW (WP1).....	25
4.	NATIONAL REVIEW OF TERMINATION OF RESUSCITATION PRACTICES (WP2) .....	27
4.1	Study design for WP2 .....	27
4.2	Data management for WP2.....	28
4.3	Data analysis for WP2.....	28
4.4	Output for WP2 .....	28
5.	ANALYSIS USING OHCAO REGISTRY DATA (WP3) .....	28
5.1	Study design for WP3 .....	28
5.2	Data collection for WP3 .....	29
5.3	Data management for WP3.....	29
5.4	Data analysis for WP3.....	29
5.5	Output for WP3 .....	30



6.	EXPERIENCES OF AND PERSPECTIVES ON PRE-HOSPITAL TERMINATION OF RESUSCITATION (WP4).....	30
6.1	Study design for WP4 .....	30
6.2	Data collection for WP4 .....	35
6.3	Data management for WP4.....	36
6.4	Data analysis for WP4.....	36
6.5	Outputs for WP4.....	37
7.	CONSENSUS CONFERENCE (WP5) .....	37
8.	ADVERSE EVENT MANAGEMENT .....	38
9.	DATA MANAGEMENT .....	39
9.1	Data collection and management .....	39
9.2	Data Management.....	39
9.3	Database.....	40
9.4	Data storage .....	40
9.5	Data access and quality assurance.....	40
9.6	Archiving.....	40
9.7	End of Study .....	40
10.	STUDY ORGANISATION AND OVERSIGHT.....	41
10.1	Sponsor and governance arrangements .....	41
10.2	Peer Review .....	41
10.3	Study Registration .....	41
10.4	Notification of serious breaches to GCP and/or study protocol.....	41
10.5	Indemnity .....	42
10.6	Study timetable and milestones.....	42
10.7	Administration.....	42
10.8	Study Management Group (SMG).....	42
10.9	Study Steering Committee (SSC) .....	42
10.10	Expert Advisory Group (EAG) .....	43
10.11	Data Monitoring Committee (DMC).....	43
10.12	Essential Documentation .....	44
10.13	Financial Support.....	44
11.	MONITORING, AUDIT AND INSPECTION .....	46
12.	PATIENT AND PUBLIC INVOLVEMENT (PPI).....	46
13.	DISSEMINATION AND PUBLICATION .....	47
14.	REFERENCES .....	50

## LIST OF TABLES

<b>Table 1</b>	Summary of Study
<b>Table 2</b>	Summaries of Main Approaches by each Work Package

## LIST OF FIGURES

<b>Figure 1</b>	PROTECTeD Project Summary
<b>Figure 2</b>	Recruitment of Participants
<b>Figure 3</b>	Project Management Plan

## LAY SUMMARY

**Aim:** To help NHS Paramedics make better decisions about when to continue and when to stop resuscitation.

**Background:** When the heart suddenly stops beating, treatment (known as resuscitation) must be started quickly. NHS Ambulance Services are called to help 30,000 people with this condition each year. Despite the best efforts of ambulance staff less than one in 10 people whose heart stops survive. This means that ambulance staff often have to make the difficult decision of when to stop resuscitation. They are helped by following guidelines, but they were written over 20 years ago and need updating.

The old guidelines no longer correctly guide paramedics when to stop treatment or when to carry on. This means that treatment may be stopped too soon in some patients who might benefit from carrying on. In other patients, the guidelines suggest to move the patient to hospital despite the fact they have no chance of surviving. The knock-on effects of this are journeys with blue lights and sirens which put ambulance staff and other road users at risk of injury from crashes. Patients are separated from their families and taken to a busy hospital. At the hospital, it is difficult for staff to allow the family to spend quiet time with the patient. Hospitals also become overcrowded which can affect other patients.

This research will develop new guidelines based on the most up to date information available. It will consider how the new guidelines might work in real life. We will find out the views of ambulance and hospital staff, patients and relatives. This will help make sure the guidelines are acceptable to everyone.

**Design:** The project involves 5 pieces of work.

1. Reviewing research undertaken by others and see how it can be used in the NHS
2. Finding out how ambulance services currently make decisions to stop or carry on with treatment
3. Seeing what the effects different guidelines may have on how ambulance staff treat patients and any knock-on effects for hospitals
4. Talking to ambulance and hospital staff, patients and relatives. This will help us find out what they think and what is important to them.
5. Combining the information above to write new guidelines. This will be done in partnership with ambulance and hospital staff, patients and members of the public.

**Patient and public involvement:** We will work closely with patients and the public to ensure that their views are fully included in the project. One of our research team is a member of the public who has personal experience of losing someone in the circumstances described here. He has worked with other patients over the years to help improve research in this area. He will work with our research team and a group of patients and members of the public to guide the research team to remain focused on the issues that are important to patients. This group will be involved in helping design, interpret and communicate the research. They will play an important role in developing the final recommendations for new guidelines.

**Dissemination:** We will publish our findings in medical journals and present them at meetings for doctors, nurses, paramedics and patients. We will send a copy of our final report to ambulance services and other interested groups. We will share the findings via the internet, our patient and public networks and through media teams, who have extensive experience of communicating such findings.

## STUDY SUMMARY

**Table 1: Summary of Study**

Study Title	Exploring and Improving Resuscitation Decisions in Out of Hospital Cardiac Arrest
Internal ref. number (or short title)	PROTECTeD
Study Design	<p>This project consists of five work packages with the following objectives:</p> <ol style="list-style-type: none"> <li>1. Describe the content and performance characteristics of existing termination of resuscitation rules in adults who are treated for out of hospital cardiac arrest.</li> <li>2. Identify areas of consistency, variation and clinical risk associated with termination of resuscitation across UK ambulance services.</li> <li>3. Examine current NHS ambulance termination resuscitation practice and model effects of alternative rules on patient flow and outcomes.</li> <li>4. Explore the perspectives of patients, relatives, paramedics and emergency medicine staff and consider the ethical aspects of termination of resuscitation rules.</li> <li>5. Synthesise the information obtained above to develop evidence based, ethically grounded, consensus guidelines, that optimizes outcomes for patients and are sensitive to needs of relatives and demands on NHS services.</li> </ol>
Study Participants	<p>WP2: Cardiac arrest leads from participating ambulance services</p> <p>WP4: Survivors of cardiac arrest/relatives of non-survivors, ambulance staff and emergency medicine staff.</p>
Planned sample size	WP4: a maximum of 30 ambulance staff and 30 ED staff, 15 survivors of cardiac arrest/relatives of non-survivors, continuing until data saturation.
Planned Study Period	<p>From: 1<sup>st</sup> July, 2019</p> <p>To: 31<sup>st</sup> May, 2022</p>

## LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
95% CI	95% Confidence Interval
AE	Adverse Event
ALS	Advance Life Support
AS	Ambulance Service
BLS	Basic Life Support
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CONSORT	<i>Consolidated Standards of Reporting Trials</i>
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
ED	Emergency Department
EMS	Emergency Medical Service
EtCO <sub>2</sub>	End-tidal Carbon Dioxide
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
IRAS	Integrated Research Application System
JRCALC	Joint Royal Colleges Ambulance Liaison Committee
kPa	Kilopascals
MD	Medical Director
MRC	Medical Research Council
NGT	Nominal Group Technique
NHS	National Health Service
NIHR	National Institute for Health Research
NLR	Negative Likelihood Ratio
NPV	Negative Predictive Value
OHCAO	Out of Hospital Cardiac Arrest Outcomes Registry

PALS	Patient Advice and Liaison Service
PI	Principal Investigator
POCUS	Point of Care Ultrasound
PPI	Patient & Public Involvement
PLR	Positive Likelihood Ratio
PPV	Positive Predictive Value
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROLE	Recognition of Life Extinct
ROSC	Return of Spontaneous Circulation
R&D	Research and Development
SAE	Serious Adverse Event
SSC	Study Steering Committee
SOP	Standard Operating Procedure
TOR	Termination of Resuscitation
UoW	University of Warwick
WCTU	Warwick Clinical Trials Unit
WP	Work Package

# 1. BACKGROUND

## 1.1 Epidemiology and burden of the condition

NHS Ambulance services respond to approximately 60,000 out of hospital cardiac arrest events each year. In approximately half of these cases the patient is obviously deceased on arrival of the ambulance crew, and resuscitation is not attempted.<sup>1</sup> However, whenever there is a chance of survival, no matter how slim, ambulance crews will always attempt resuscitation.<sup>2</sup> Unfortunately, the majority of resuscitation attempts are unsuccessful. Paramedics cease resuscitation efforts in the field in approximately 10,000 cases, and transport the remaining 20,000 patients to hospital (14,000 with CPR in progress and 6,000 after return of spontaneous circulation (ROSC)). Among all the patients where resuscitation is attempted, only 7-8% will survive to hospital discharge.<sup>1</sup>

The decision to cease resuscitation or transfer to hospital is informed by the national Recognition of Life Extinct (ROLE) guideline.<sup>2</sup> A key purpose of the ROLE guideline is to distinguish between those patients who have no chance of survival, where resuscitation efforts can be safely discontinued without transfer to hospital, and those patients with any chance of survival, no matter how slim, where transport to hospital, to avail the patient of the additional resources and expertise, is indicated. The ROLE criteria were implemented over 20 years ago based on expert opinion and anecdotal clinical experience.

## 1.2 Existing knowledge

A number of different approaches exist to determine when on-going resuscitation efforts have negligible chance of success. These can be broadly classified as (i) time based considerations , (ii) those based on the clinical characteristics of the patient and their response to treatment and (iii) those which use ancillary tests. The benefits of transfer with on-going CPR are uncertain with some evidence suggesting it may be harmful. There is a paucity of evidence concerning what impact discontinuing resuscitation at the scene has on relatives and care providers.

### *Time based decisions*

The Recognition of Life Extinct (ROLE) guideline (based on the European Resuscitation Council termination of resuscitation rule)<sup>2</sup> combines cardiac arrest event characteristics (asystole) with a failure to respond to treatment within 20 minutes of the initiation of advanced life support. Under this guideline patients who continue to have evidence of electrical activity on the ECG (including agonal heart rhythm, slow pulseless electrical activity) are recommended for transport to hospital.

There have been no published evaluations of the performance of the ROLE guideline in the UK. The ROLE guideline was retrospectively applied to a cohort of patients enrolled in the Swedish Cardiac Arrest Registry (1990-2007). The rule was 95% sensitive (95% CI: 91.3–97.5) and 99.9% specific (95% CI: 99.9–99.9) for identifying cases where on-going resuscitation efforts were not associated with long term survival .<sup>3</sup> In order to correctly validate termination of resuscitation rules, all patients to whom the rule is applied must be transported regardless of the decision the rule indicates. This and many other retrospective studies of this nature are limited as protocols in place at the time already allowed termination of resuscitation (in this study after 30 minutes). This runs the risk of a phenomenon referred to as self-fulfilling prophecy bias – knowledge of the test result leads to termination of resuscitation. This trial was also limited by the inclusion of data that are over 25 years old. Resuscitation practice and outcomes have improved since the study was published which may limit generalisability to current day practice.<sup>1,4</sup>

A secondary analysis of 11,368 patients enrolled the US based ROC-PRIMED trial identified that 90% of patients with favourable neurological outcomes achieved initial return of spontaneous circulation within 20 minutes and 99% within 37 minutes.<sup>5</sup> There were no survivors with favourable neurological outcome where ROSC occurred after 47 minutes irrespective of initial rhythm. Similar studies examining resuscitation duration amongst bystander witnessed cardiac arrest cases in Japan identified that it took 40-45 minutes of resuscitation before 99% of survivors with favourable neurological outcome were identified.<sup>6,7</sup> These studies challenge the current 20 minute cut off which is used as part of the UK ROLE guideline and suggest there may be additional benefit from continuing resuscitation efforts for longer.

### ***Cardiac arrest characteristics and response to treatment***

Alternatives to time based rules are rules relating to the clinical characteristics of patients and response to treatment. We identified 9 such decisions rules.<sup>3,8-16</sup> These vary in complexity from failure to achieve pre-hospital ROSC to decisions tools with 5 or more criteria.<sup>10,16,17</sup> Application of different termination of resuscitation rules affects the proportion of patients transported to hospital (range 47% to 94%) as well as the number of survivors.<sup>18-20</sup>

For example, Morrison et al developed, validated and then tested the implementation of basic and advanced life support (BLS) termination rules. The BLS rule identified patients for termination of resuscitation efforts if the arrest was not witnessed by ambulance staff, no shocks were required and no return of spontaneous circulation was achieved during the resuscitation attempt. The prospective evaluation of the BLS termination rule identified a specificity of 90.2% (95% CI 88.4–91.8) for identifying potential survivors and a positive predictive value (PPV) of 99.5% (95% CI 98.9–99.8) for death.<sup>28</sup> It reduced the transport rate by 37.4%. The addition of Emergency Medical School (EMS) response time greater than 8 minutes improves specificity to 97.6% (95% CI 96.5–98.3), PPV for death is 99.7% (95% CI 99.2–99.9) and the transport rate reduced by 68.4%. When ‘cardiac arrest not witnessed by a bystander’ is added, specificity improved to 100% (95% CI 99.6–100) and the PPV for death was also 100% (95% CI 99.6–100); the transport rate reduced a further 61.6%. Subsequent studies in other settings confirmed the tools performance<sup>10,21</sup>.

In preparation for this application we conducted a 3 centre, retrospective evaluation of patients transported to hospital with on-going CPR in the West Midlands.<sup>22</sup> During the 14 month study period (September 2016 and November 2017) 227 patients (median age 69 years, 67.8% male) were transported to hospital with on-going CPR. Of these 227 patients, 89 (39.2%) met the Morrison termination of resuscitation criteria. After hospital arrival, patients received few specialist interventions that were not available in the prehospital setting. Most (n = 210, 92.5%) died in the emergency department. Only 17 were admitted to hospital (14 to intensive care), of whom 3 (1.3%) survived to hospital discharge. There were no survivors (0%) among those who met the criteria for Morrison termination of resuscitation criteria.

### ***Ancillary tests***

End-tidal carbon dioxide (EtCO<sub>2</sub>) can be measured non-invasively through a sensor attached to an advanced airway. The technology has been routinely available in NHS Ambulance Services for the last five years and is generating interest as a prognostic tool in cardiac arrest. End-tidal carbon dioxide levels are related to cardiac output and pulmonary blood flow and is considered an indirect indicator



of coronary perfusion pressure. Low levels of EtCO<sub>2</sub> are commonly seen during cardiac arrest, reflecting the comparatively low cardiac output provided by CPR. The level of EtCO<sub>2</sub> is also affected by the cause of cardiac arrest, the quality of chest compressions, ventilation rate and volume, time from cardiac arrest and the use of drugs. Observational studies have found associations between high (or rising) levels of EtCO<sub>2</sub> and ROSC and between low levels (< 1.3kPa) and a failure to achieve ROSC.<sup>23,24</sup> However there is uncertainty about the utility of these measurements and whether they can aid clinical decision making about the continuation of resuscitation.<sup>25</sup>

Point of care ultrasound (POCUS) allows real-time imaging of the heart during CPR. A 2017 systematic review and meta-analysis<sup>26</sup> of 15 studies involving 1,695 cardiac arrest patients reported that cardiac wall motion detected by POCUS had a pooled sensitivity of 95% (95%CI: 72–99) and specificity of 80% (95%CI:63–91) in predicting ROSC during cardiac arrest, with a positive likelihood ratio of 4.8 (95% CI: 2.5–9.4) and a negative likelihood ratio of 6% (95%CI: 1–39). With advances in technology the size and cost of point of care ultrasound has reduced and the technology is being slowly adopted by some NHS ambulance services. Although an attractive concept, imaging by paramedics outside a hospital may be limited by poorer image quality.<sup>27</sup> In addition, obtaining an ultrasound image may lead to harmful interruptions to chest compressions.<sup>28</sup> Before widespread adoption of this technology there is a need to consider the performance characteristics of clinical decision rules which include ultrasound.

### ***Harms from transfer with CPR in progress***

There is an increased risk of injury associated with ambulance transport with blue lights and sirens<sup>29-35</sup>. In the UK, there are in excess of 300 ambulance accidents, resulting in over 500 injured and 3-5 fatalities each year<sup>36</sup>. In addition, quality of CPR is also adversely impacted due to interruptions in CPR as the patient is transferred from scene into the ambulance, and during the journey to hospital due to off-balancing forces experienced by the paramedic performing CPR secondary to breaking, acceleration and turning of the ambulance.<sup>37,38</sup>

Published data indicate that prehospital ROSC is the single largest determinant of patient survival to hospital discharge, with one study reporting a 99.6% NPV.<sup>18,39</sup> The evidence suggests therefore that EMS should focus efforts to achieve ROSC on scene and be very selective with respect to which patients might benefit from transport to hospital with ongoing resuscitation.

### ***Clinicians' and relatives' preferences***

Clinicians find performing resuscitation where it has little chance of success distressing.<sup>40</sup> This may in part be through the perception of infliction of physical abuse on the dead or dying patient.<sup>41,42</sup> Relatively little primary research exists on clinicians preferences on continuing versus terminating resuscitation in the field rather than transfer in to hospital. The limited available evidence suggests that family conflict with decision,<sup>43,44</sup> public location of the cardiac arrest<sup>44,45</sup> and medicolegal concerns<sup>44</sup> may limit the use of termination of resuscitation rules. Facilitators to applying termination of resuscitation rules included paramedic psychological comfort,<sup>45</sup> experience,<sup>45</sup> knowledge of survival outcomes,<sup>45</sup> education<sup>46</sup> and a structured ethical framework.<sup>47</sup>

We were only able to identify limited research (none of which originated in the UK) on patients and relatives preferences for where resuscitation should be discontinued, when it is clear there is no chance it will be successful.<sup>48,49</sup> Although end of life care guidelines suggest many patients prefer to die at home, a

recent systematic review suggests the evidence supporting that assertion is limited.<sup>50</sup> These data highlight the need for further primary research about patients, relatives and clinicians preferences for when and where to discontinue resuscitation efforts.

### **1.3 Research Question**

In adult patients who sustain an out of hospital cardiac arrest and do not respond to treatment by paramedics, what is the best approach for deciding when and where to stop resuscitation attempts?

### **1.4 Need for a study**

Advances in clinical practice and new scientific evidence suggests that the ROLE guideline may no longer be fit for purpose. Specifically:

- i. The ROLE guideline allows paramedics to discontinue resuscitation after as little as 20 minutes. Recent evidence indicates resuscitation should continue for at least 40 minutes, suggesting potential survivors may be missed by stopping too soon.<sup>7,51-53</sup>
- ii. Ineffective CPR reduces the likelihood of survival. Several studies have reported that it is challenging to perform high quality CPR in a moving ambulance. Transporting patients while performing CPR therefore risks sub-optimal treatment.<sup>37,54</sup>
- iii. Advances in the monitoring equipment used by paramedics now means additional physiologic parameters can be measured, for example end tidal carbon dioxide (EtCO<sub>2</sub>). There is a growing body of observational data to indicate persistently low EtCO<sub>2</sub> is associated with a very poor prognosis.<sup>23,24</sup> The ROLE guideline does not take into account such advances in paramedic monitoring capabilities, and recommends transport of patients who have will negligible chance of survival.
- iv. Alternative termination of resuscitation rules have been developed and validated in several countries (for example the Morrison Universal Termination of Resuscitation Rule) that may better predict who will not survive their cardiac arrest event.
- v. There is growing concern that inappropriate transfer with lights and sirens places ambulance staff and other road users at increased risk of road traffic collision.<sup>36,55</sup>
- vi. Emergent transfer to hospital of patients with no chance of survival separates the patient from their family and moves them from home / the community into hospital to overstretched emergency departments (ED).
- vii. The development of regional networks of Cardiac Arrest Centres will necessitate longer ambulance journeys for victims of cardiac arrest to fewer specialist centres. Accurate identification of potential survivors will be paramount to prevent overwhelming them.

Concerns about the ROLE guideline have led individual ambulance services to modify practices locally, thus increasing variation in practice based on geographical location. Given the above, it is now essential to review the provision of services by ambulance services for victims of cardiac arrest. This research is essential for several reasons:

### ***Health need***

We may be allowing as many as 300 people a year to die unnecessarily from terminating resuscitation too early.<sup>53</sup> By contrast, the un-selective transfer of 20,000 patients per year with ongoing CPR is

resource intensive at times of growing pressure on emergency services and places ambulance staff and others at risk of death or serious injury.<sup>36</sup>

### ***Expressed need***

This proposal is highly relevant to the needs of patients and the NHS. This need is articulated through:

- (i) National policy documents that place a high priority on improving survival from cardiac arrest
- (ii) A desire to deliver the right care to the right patient at the right time
- (iii) The drive to reduce variation in the NHS as a whole and specifically within ambulance services
- (iv) The government's commitment to improve end of life care
- (v) The need to optimise emergency care pathways to reduce ED overcrowding and deliver better care
- (vi) NHS Ambulance Cardiac Leads Group prioritising this subject as one of the most important areas for further research.

### ***Sustained interest and intent***

As the number of cardiac arrests increases year on year and demand on acute services continues to grow, the results of this research will remain highly relevant and important to the needs of the NHS in the future.

### ***New knowledge***

Health systems from which existing data are derived differ from the UK setting (e.g. the US use a two tier ambulance response system, in Asia, paramedics are not allowed to terminate resuscitation). Very little information is known about patient and relatives experience. This creates the specific need to generate new knowledge that is embedded in and generalisable to the NHS.

### ***Generalisability and prospects for change***

This work will draw on NHS data to quantify and model the effect of new approaches to resuscitation decision making on patient flow and outcomes. It will seek the views of front line NHS clinicians from the ambulance and hospital setting and senior staff within ambulance services. It will explore, for the first time, the perspectives of relatives of victims of cardiac arrest, treated by the NHS. It will develop new treatment pathways in partnership between patient and public representatives and ambulance services.

Through our close association and leadership roles within organisations responsible for NHS clinical practice guidelines (Resuscitation Council (UK) and Association of Ambulance Medical Directors) it is highly likely the research findings will improve decision-making and bring about change and improvement.

### ***Building on existing work***

This proposal builds directly on our previous HSDR funded projects related to resuscitation decisions and emergency care treatment plans (15/15/09) and our evaluation of cardiac arrest pathways in the NHS (11/2004/30). It links indirectly on our gate keeping in intensive care project (13/10/14). It will make use of the national cardiac arrest outcomes registry funded by charitable partners and hosted by the University of Warwick, improving efficiency and reducing costs. It aligns with our plans for an acute care interfaces workstream as part of the West Midlands CLARHC.

### **1.5 Ethical considerations**

The study will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation) and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with UK legislation.

We will complete all necessary research permissions through the Health Research Authority and necessary processes with participating NHS sites and associated Trusts. The study will be conducted in accordance with the principles of the UK Policy Framework for Health and Social Care Research. General monitoring of study conduct and data collected will be performed by a combination of central review and monitoring by quality assurance staff from Warwick CTU on behalf of the Sponsor.

We will seek Research Ethics Committee approval during the first three months of the study, in readiness for WP4. Ethical issues in this project concern i) identification of victims of cardiac arrest ii) identification of relatives of victims of cardiac arrest iii) identification of staff caring for victims of cardiac arrest iv) obtaining informed consent for participation in interviews v) potential distress caused by interviews.

Some of the work described in this protocol crosses the interface between research and service evaluation and is of a mixed methods design. The research involves four main activities, which are ordered to reflect their invasiveness:

- 1) Interviewing patients, relatives and clinicians
- 2) Use of anonymised data from the OHCAO registry
- 3) Review of local policies and guidelines
- 4) Review and analysis of published literature

#### **1) *Interviewing patients, relatives and clinicians (WP4)***

The consent process for interviews will follow standard models for obtaining written or verbal informed consent and will be required for all individuals who agree to participate. Additional detail can be found in individual work packages.

We will be interviewing families, and survivors about a very difficult and emotional experience. During our initial recruitment of sites we will identify the available support services in the hospital for survivors of cardiac arrest and their families, and identify local contacts for bereavement support, for families of non-survivors. We will provide contact details of these support services to participants as well as details of local and national support groups. Interview participants will be reassured that they can stop the interview at any time and if the participant shows signs of distress during the interview the interviewer will stop the interview. If the researcher is concerned about a significant harm for an individual participant, for example

if the participant discloses a suicidal intention, the researcher will discuss this immediately with the WP lead for WP4 who will contact the participant to assess the situation and ensure that appropriate support is provided (see disclosures of confidential information below).

It is possible that a patient or family member may indicate to the researcher that they wish to make a complaint about patient care. In this situation the researcher will direct them to the relevant NHS Trust's complaints procedure and the trusts PALS service.

The researcher conducting the interviews will receive appropriate training to ensure they are able to conduct interviews in a sensitive and professional manner. The researcher will also will have regular debriefing meetings with the leads for WP4 (AS or FG) each week throughout data collection.

This subject may be distressing for ambulance and hospital staff to talk about. As with survivors and families of non survivors the researcher will reassure them they can stop the interview at any time. We will also provide contact details of support services for staff within the relevant Ambulance and Acute Trust (see disclosures of confidential information below).

If concern arises about unethical or unsafe clinical practice the researcher will consult the WP leads (FG or AS) who, in consultation with the Chief Investigator will decide if it is necessary to initiate action through normal professional channels, which is likely to be through the relevant NHS Trust. We think it is unlikely that serious unprofessional conduct will be observed or disclosed in this study. If any disclosures are made the participant involved in the interview where this practice was revealed (clinician or family member) will be informed that this is happening. The need for a researcher to disclose any evidence of serious professional misconduct will be made clear in the relevant participant information sheets.

## ***2) Use of anonymised data from the OHCAO registry***

Anonymous information will be sent securely from the OHCAO team under the terms and conditions of a data sharing agreement. OHCAO hold this information with permission from Research Ethics Committee (REC) reference: 13/SC/0361 and Confidentiality Advisory Group (CAG): reference: ECC 804 C/2013.

## ***3) Review of local policies and guidelines***

There are no ethical concerns that need to be addressed.

## ***4) Review and analysis of published literature***

There are no ethical concerns that need to be addressed to review the published literature

## **2. STUDY DESIGN**

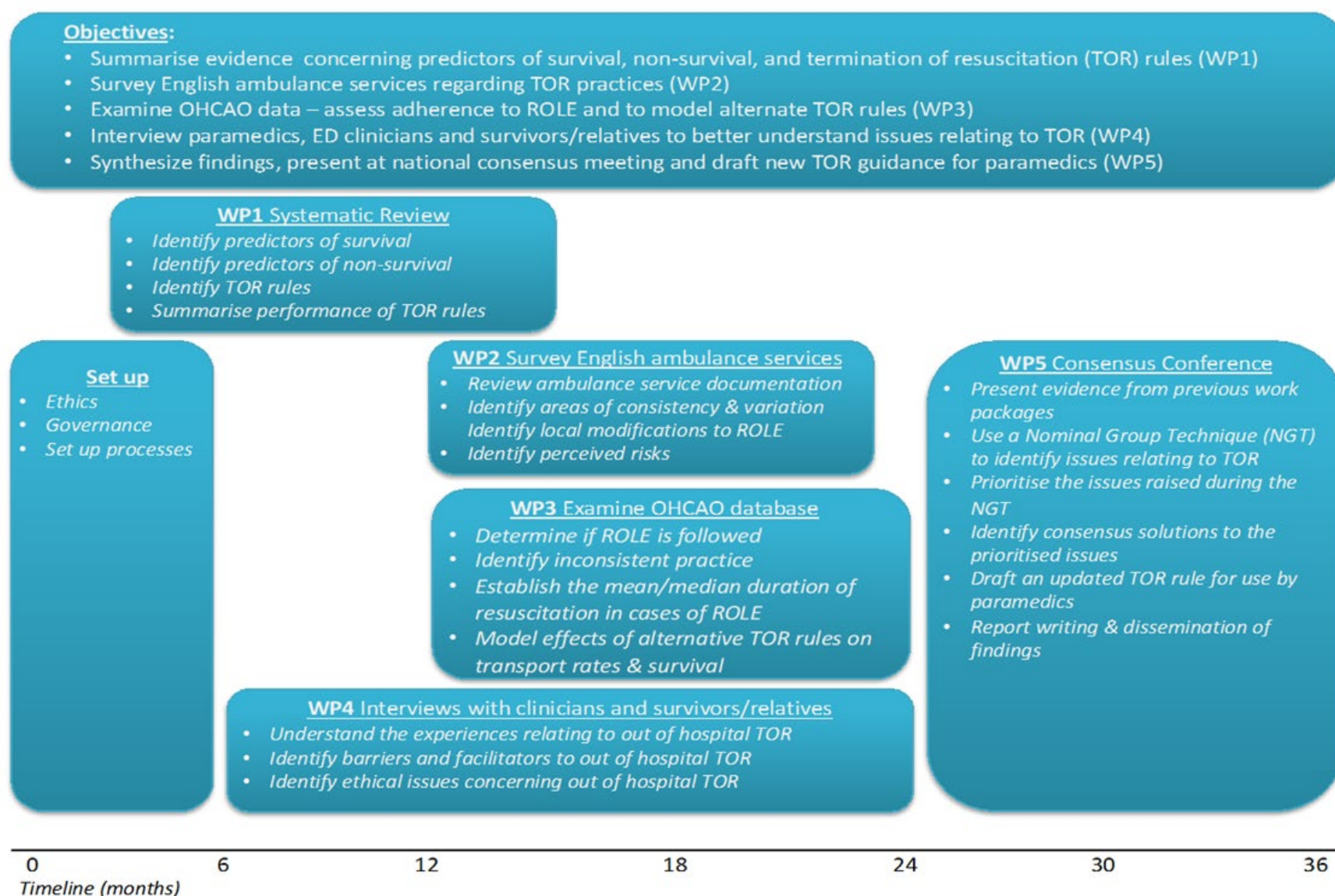
### **2.1 Study summary and flow diagram**

This is a mixed-methods, study to establish the clinical criteria to indicate that continuing resuscitation is futile; when the decision to discontinue resuscitation should be made; who should make the decision and where the decision should be made, among adult out of hospital cardiac arrest patients who do not respond to resuscitation efforts.

This section presents an overview of the study, its ethical considerations and procedures across the five work packages (WPs). Details of the individual WPs are following in sections 3 (WP1), 4 (WP2), 5 (WP3), 6 (WP4) and 7 (WP5).

The study consists of five WP's with the following objectives:

**Figure 1: PROTECTeD Project Summary**



## **2.2 Aims and objectives**

### **2.2.1 Primary objective**

To develop an evidence based guideline that assists paramedics, when making decisions during out of hospital cardiac arrest that optimises outcomes for patients and is sensitive to needs of relatives and demands on NHS services.

### **2.2.2 Secondary objective**

Study flow diagram is shown in figure 1:

- WP 1: Describes the content and performance characteristics of existing termination of resuscitation rules in adults who are treated for out of hospital cardiac arrest.
- WP 2: Identifies areas of consistency, variation and clinical risk associated with termination of resuscitation practices across the UK ambulance services.
- WP 3: Examines current NHS ambulance termination of resuscitation practice and model effects of alternative rules on patient flow and outcomes.
- WP 4: Explores the perspectives of patients, relatives, paramedics and emergency medicine staff and consider the ethical aspects of termination of resuscitation rules.
- WP 5: Synthesises the information obtained above to develop evidence based, ethically grounded, consensus guidelines, that optimise outcomes for patients and are sensitive to the needs of relatives and the demands on NHS services.

## **2.3 Recruitment Summary**

Work packages 1, 2, 3 and 5 will not be recruiting participants.

Work package 4:

Recruitment within WP4 will continue until we have interviews with a maximum of 30 ambulance staff and 30 ED staff, continuing until data saturation. We expect to recruit approximately 15 patient/family members for interviews who had direct experience of the cardiac arrest (for family members this means they were present at the time of the arrest and treatment by the ambulance crew/hospital staff). Interviews may also include family members who express interest in the study but were not present at the event. We expect up to 5 of these interviews. The number of cardiac arrest events may be more than 20 as not all stakeholders will be involved in any one event. The maximum number of cardiac arrest events will be 75.

## **2.4 Eligibility criteria**

Participants are eligible to be included in the study (WP4) if they fall in the categories outlined in 2.3 above.

### **2.4.1 Exclusion criteria**

1. Lack of provision of informed consent (written or verbal)
2. Aged under 18



3. Known to be a prisoner

### 3. SYSTEMATIC REVIEW (WP1)

*Aim:* To describe the characteristics and performance of termination of resuscitation rules in adults who are treated for out of hospital cardiac arrest.

*Objectives:*

- Identify the content and structure of existing termination of resuscitation rules
- Summarise performance characteristics of termination of resuscitation rules

*Plan of Investigation:* The protocol for the systematic review will be registered with the International Prospective Register of Systematic Reviews (CRD42019131010). It will be conducted in accordance with recommendations from the Cochrane Screening and Diagnostic Tests Methods Group and reported in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement.<sup>56</sup>

*Search Strategy:* Systematic searches of MEDLINE, EMBASE, CINAHL, EconLit, Web of Science and the Cochrane Database will be performed. Search strategies, combining MeSH terms and Key Word searching, will be developed in collaboration with a medical information specialist. Quality assurance strategies will include ensuring key papers are retrieved, reviewing the reference lists of included papers and contacting subject experts.

*Study Selection:* Studies will be included based upon a-priori defined inclusion/exclusion criteria. Two reviewers will independently evaluate each study identified against the inclusion/exclusion criteria. Where reviewers disagree, a third reviewer will adjudicate. Kappa statistics will be reported for reviewer agreement.

*Inclusion Criteria:*

- Language: No language restrictions will be placed. It is expected that a small proportion of non-English citations will be identified. Where such studies are identified, we will contact the author to ask if an English translations is available. If no English translation is available from the author we will attempt to obtain a translation by informal methods. Where informal methods fail, we will exclude the study. Google translate (or similar engine) will not be used to translate non-English citations. A record of non-English citations will be maintained to gauge how much potential evidence has been excluded from the systematic review.
- Publication type: original research published in peer reviewed journals.
- Study Design: systematic reviews, meta-analyses, randomised controlled trials, case-control studies, cohort studies, cross-sectional studies, retrospective analyses, economic evaluations, modelling studies.
- Study Population: adult patients suffering out-of-hospital cardiac arrest.
- Intervention/s: termination of resuscitation rules.
- Comparators: alternative rules, usual care and/or standard practice.
- Outcomes: performance characteristics of identified termination of resuscitation rules.

- Setting: out-of-hospital.
- Timing: all-cause mortality up to 30 days or hospital discharge.

#### *Exclusion Criteria:*

- Publication type: narrative reviews, letters, editorials, commentaries, books and book chapters, lectures and addresses and consensus statements.
- Study Design: case reports and/or studies that fail to report their methods.
- Study Population: in-hospital studies and/or animal studies.

The systematic review process will consist of data being extracted independently by one reviewer using standardised definitions. Data extracted will be documented and independently checked for accuracy by a second reviewer. Uncertainties will be resolved by discussion. Those that cannot be resolved will be referred to the rest of the project team. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

The methodological quality of each included study will be assessed by one reviewer and checked by a second. A critical appraisal tool appropriate to study design will be utilised to assess the quality of each included study. Risk of bias will be assessed using the ROB-2 instrument for randomised controlled trials<sup>57</sup> and ROBINS-I instruction for non-randomised trials<sup>58</sup> as per recommendations of the MRC Network Hubs for Trials Methodology Research. An adapted QUADAS-2<sup>59</sup> will be used to assess studies of diagnostic accuracy and PROBAST<sup>60</sup> will be used to assess prediction modelling studies. The CHEERS checklist<sup>61</sup> will be used to assess the quality of economic evaluations. Quality of evidence will be reported as per GRADE working group recommendations.<sup>62</sup>

The following standardised data will be extracted from each eligible study: study design, date of study and sample size, population characteristics (age, gender, cause of cardiac arrest, initial rhythm, bystander response), setting (location and ambulance service characteristics), characteristics of termination of resuscitation tools (index test) and reference standard, resuscitation outcome (termination of resuscitation, transport to hospital, return of spontaneous circulation) and patient outcome (died, survival (to discharge or 30 days)). If appropriate, the authors of the primary studies will be contacted for missing data. We will assess and tabulate sources of variability (multiple definitions of target condition, different definitions termination rules, clinician applying the rule, differences in reference standard, handling indeterminate test results, grouping and comparing tests).

*Analysis:* We are aware of the discordance in published studies as to whether survival or death is used as the positive outcome when defining diagnostic test performance and the challenges this creates for summarizing the evidence and presenting it in a meaningful way to ambulance services. We will adopt the recommendations from Morrison that death is treated as the positive outcome (i.e. the termination of resuscitation rule correctly classifies all those who have no chance of survival).<sup>63</sup> We will derive or convert study findings to enable consistent reporting of diagnostic test performance in a 2 by 2 table and calculate sensitivity, specificity, positive predictive value and negative predictive value and their 95% confidence intervals. We will plot the data for each of these statistics to illustrate the best cut-off values. Results examining theoretical application of termination of resuscitation rules will be examined separately from studies examining implementation of termination rules in 'real life'. In the event that a meta-analysis is not appropriate a narrative synthesis will be performed including: level of accuracy, precision of results and consistency of findings across studies. If robust diagnostic test accuracy studies at low risk of bias with homogenous study populations, design and definitions are retrieved, a quantitative synthesis will be

considered to give pooled sensitivity and specificity estimates, stratified by triage tool. Study specific estimates of sensitivity and specificity will initially be compared in coupled Forest plots and if relevant summary receiver operating curves.<sup>64,65</sup> Variability will be assessed systematically. In the absence of variability, a hierarchical random effects bivariate model will be used for binary index tests to calculate summary values for sensitivity and specificity, with associated 95% confidence intervals.<sup>64,65</sup> The results of the economic evaluations will be reported in the form of a narrative synthesis. Informed by the retrieved studies the following post hoc analyses may be performed: investigating heterogeneity (meta-regression models); comparing the performance of different triage tools (a multilevel bivariate model or the Rutter and Gatsonis HSROC method) and sensitivity analyses examining the effect of methodological quality and differing study population or settings.<sup>64,65</sup> Reporting biases will be evaluated using Deek's method of examining effective sample size funnel plots with associated regression test of asymmetry used to detect publication bias and other sample size related effects.<sup>66</sup> However, the limitations of methods to detect publication bias in diagnostic accuracy data are acknowledged.

*Output:* We will publish a manuscript with clear description of the study background, methods and results, presented in accordance with Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies.<sup>56</sup> It will summarise the performance characteristics (sensitivity, specificity, negative and positive predictive values) for termination of resuscitation rules among adults who sustain an out of hospital cardiac arrest and their influence on transport rates. The overall strength of supporting evidence will be reported in accordance with GRADE system.<sup>62</sup>

Insufficient evidence will be highlighted if conclusions cannot be drawn because there are too few reliable studies, or too much uncertainty.

## **4. NATIONAL REVIEW OF TERMINATION OF RESUSCITATION PRACTICES (WP2)**

### **4.1 Study design for WP2**

*Aim:* Identify areas of consistency, variation and clinical risk associated with termination of resuscitation practices across UK ambulance services.

*Objectives:*

- Review the policies, procedures, clinical notices and education packages relating to termination of resuscitation in each ambulance service
- Identify areas of consistency and variation, in resuscitation practices between ambulance services
- Identify local modifications to the ROLE guideline by each ambulance service
- Determine how policies and procedures for termination of resuscitation are implemented in each ambulance service
- Understand the organisational risks associated with providing resuscitation services, as perceived by senior personnel in each ambulance service

*Plan of investigation:* We will ask each ambulance service to provide copies of all documents (policies, procedures, clinical notices, operational notices, briefings, training notices and any education and

training materials) relating to termination of resuscitation by ambulance staff within their trust. We will then undertake a document analysis to examine consistency and variation in termination of resuscitation practices between ambulance services. We will specifically look for evidence of local modifications to the national ROLE guidance. We will further explore the timing, structure and content of relevant education packages relating to termination of resuscitation.

Finally, we will present our findings to a meeting of the National Leads Group and invite their feedback to identify those areas of clinical practice relating to cardiac arrest decision making that they believe are most challenging for ambulance services and to explore perceived organisational risks and concerns associated with the current ROLE guidelines.

#### **4.2 Data management for WP2**

Any documents supplied by ambulance service collaborators will be managed in accordance with WCTU policies and procedures. Contemporaneous notes taken during meeting where our findings are presented to the National Leads Group will be stored in accordance with WCTU policies and procedures. No audio recordings will be made.

#### **4.3 Data analysis for WP2**

Findings will be collated and tabulated to present a national overview of current policies, training and implementation of termination of resuscitation.

#### **4.4 Output for WP2**

*Output:* Understanding of consistency and variation in resuscitation practices and clinical risk concerns among ambulance services.

### **5. ANALYSIS USING OHCAO REGISTRY DATA (WP3)**

#### **5.1 Study design for WP3**

*Aim:* Examine current NHS ambulance termination of resuscitation practice and model effects and cost effectiveness of alternative rules on patient flow and outcomes

*Objectives:*

- Analyse the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry data to describe current practice across ambulance services in England and Wales.
- Model the effects and cost-effectiveness of alternative termination of resuscitation rules on both transport rates and survival to hospital discharge.

*Plan of investigation:* we will use the OHCAO registry which collects information from all English and the Welsh Ambulance Services on patients who are treated by ambulance personnel for an out of hospital cardiac arrest. The registry, hosted by the University of Warwick, is structured and maintained in accordance with the Utstein Guidelines for resuscitation registries,<sup>67</sup> and details of it have been summarised previously.<sup>68</sup> The National Research Ethics Service granted ethics approval, reference number 13/SC/036. The Confidential Advisory Group (CAG), reference number ECC8-

04C/2013, granted approval to use identifiable patient information where it is not practical to obtain consent.

*Sample size:* Using the registry data and taking the lowest prevalence (most conservative) of 18%, from the three outcomes (recognised of life extinct, ROSC at hospital handover and CPR transported to hospital), a sample of 94, 000 patients would be required to detect 0.0015 precision in maximum clinically acceptable width of the 95% confidence interval of both the sensitivity (true positives) and specificity (true negatives). This sample size would also allow a test sensitivity of 99% to be detected using 5% as the type I error rate. We anticipate that the number of cases in the registry (during 2014-2018) will be approximately 132,000 and therefore our sample will provide very accurate estimates of sensitivity and specificity, in relation to the population

*Withdrawals and exclusions:* WP3 is using routinely collected anonymised data from the OHCAO registry. Any concerns patients had about their anonymised information being included, should have been addressed by the organisation collecting the data at the time. Withdrawal will not be possible from the anonymised data provided to the study team.

## **5.2 Data collection for WP3**

*Data collection:* The OHCAO registry collects data on individual patient demographic, cardiac arrest event characteristics, ambulance response times, treatments administered, response to treatment, whether the patient was transported to hospital with or without ongoing CPR, whether and when return of spontaneous circulation was achieved and the final outcome (survival to hospital discharge). The database currently has information from over 150,000 cases of out of hospital cardiac arrest.

## **5.3 Data management for WP3**

*Data management:* Data will be sent securely from the OHCAO Registry in an anonymised format, in accordance with Warwick SOPs. Data sharing will follow OHCAO processes. No formal data sharing agreement is required due to the University of Warwick being the legal entity for both the OHCAO Registry and PROTECTeD project.

## **5.4 Data analysis for WP3**

*Data quality checks:* data quality checks are performed within the OHCAO study according to the OHCAO protocol, which includes data being validated by the OHCAO web application upon submission from the AS and annual data cleaning, prior to the transfer of the clean anonymised data set to PROTECTeD study for analysis.

*Data analysis:* We will use descriptive statistics to summarise current practice by reporting patient characteristics (age, gender), cardiac arrest characteristics (cause, initial rhythm, witness status, bystander CPR), hospital transfer rates and survival status according to whether (a) resuscitation was terminated on scene, (b) return of spontaneous circulation was achieved or (c) the patient was transported to hospital with on-going CPR. We will estimate costs based on data from the PARAMEDIC2 trial.<sup>69</sup> Results will be presented individually for each of the English and Welsh Ambulance Services. We will calculate the proportion of patients who fulfilled the national ROLE criteria for each ambulance service and whether resuscitation was terminated at scene or the patient was transported to hospital to highlight any discordance between policy and practice. We will describe the number and characteristics of patients where resuscitation was discontinued at the scene but they did not fulfil the

termination of resuscitation criteria. We will also report exceptions where the termination of resuscitation criteria indicated resuscitation would be unsuccessful but the patient survived.

We will model the impact of alternative termination of resuscitation rules identified in WP1 and report the impact of their use on the proportion of patients in whom resuscitation would be discontinued at the scene versus transport in to hospital. We will examine the performance of the different rules by calculating the sensitivity, specificity, positive predictive value, negative predictive value and their 95% confidence intervals for each of the alternative TOR rules. We will use the current JRCALC ROLE guideline as the gold standard. In order to determine the significance of the difference in sensitivity and specificity of each of the alternative TOR rules, statistical evaluation will be performed using appropriate tests, e.g. McNemar test with Yates Correction. We will compare model performance by performing a ROC analysis and analyse differences in test performance using De Long's method for comparing c-statistics.

We are aware that our approach will be confounded by the self-fulfilling prophecy bias outlined above. However, the intention of this work package is to compare alternative rules to current national guidelines. These risks are therefore less relevant than if we claimed to be under taking an independent evaluation of alternative rules.

We will additionally develop a decision-analytic model that will estimate the cost-effectiveness of the current JRCALC ROLE guideline and alternative termination of resuscitation rules. The model will be informed by data extracted from the OHCAO registry data as well as data identified in the published literature, including data identified in WP 1. Cost-effectiveness will be expressed in terms of incremental cost per additional survivor to hospital discharge. Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis, and the probability of cost-effectiveness of each strategy shown in cost-effectiveness acceptability curves.

### **5.5 Output for WP3**

*Output:* An overview of resuscitation practice and compliance with the current ROLE guideline in England and Wales and an assessment of the potential impact of alternate termination of resuscitation rules.

## **6. EXPERIENCES OF AND PERSPECTIVES ON PRE-HOSPITAL TERMINATION OF RESUSCITATION (WP4)**

### **6.1 Study design for WP4**

*Aim:* Explore the perspectives of patients, relatives, paramedics and emergency medicine staff and consider the ethical aspects of termination of resuscitation rules.

*Objectives:*

- Understand the experiences of those impacted by decisions concerning out of hospital termination of resuscitation
- Identify the challenges for paramedics faced with out of hospital termination of resuscitation decisions

- Explore the values, beliefs and preferences of cardiac arrest survivors, families, paramedics and emergency medicine staff concerning out of hospital termination of resuscitation.
- Identify the ethical considerations related to out of hospital termination of resuscitation decisions.

*Plan of investigation:* We will undertake semi-structured interviews with three distinct groups:

- Survivors of cardiac arrest/relatives of survivors and non-survivors
- Ambulance staff
- Emergency medicine staff

*Setting:* Up to three ambulance services and two Emergency Departments (EDs) within the area covered by each service. Within each participating ambulance service, we will identify a busy urban ED and a less busy rural/suburban ED.

*PPI and study advisory group involvement:*

Early in the study the PPI and study advisory group will work with the project team to develop vignettes for use in the interviews. These will represent common and more unusual cardiac arrest scenarios where a decision to continue/not continue resuscitation was made. During data analysis we will engage these groups with interpretation of our data and seek their advice on presentation of data for dissemination.

*Recruitment:*

We will visit ambulance services who express an interest in participating in the qualitative study. In collaboration with our ambulance service partners we will identify EDs that could be potential collaborators. We will approach the lead doctor and / or nurse of the identified EDs and arrange to visit the department to explain the study. We will provide potential collaborating EDs with information about the study for them to share with staff likely to care for patients who have suffered an out of hospital cardiac arrest. In each organisation that expresses an interest to participate we will secure the necessary approvals via their respective Research and Development Department.

*Ambulance staff:*

Participating ambulance services will identify individual cardiac arrest cases where ROLE is performed and patients do not get transported to hospital. Paramedics who performed ROLE will be identified by the research paramedic, as soon after the event as practicable, and invited to participate in the study via their work email from the Ambulance Service PI (or their delegate). The email/letter of invitation will include information about the study. Paramedics interested in the study will be asked to contact the research team to discuss the study and arrange an interview. Verbal consent to retain contact details will be confirmed when an interview is scheduled. A study information sheet will be posted/emailed to the potential participant prior to the interview. Formal consent will be obtained on the day of the interview before the interview starts. Consent will be written where interviews are face to face, and audio-recorded where held remotely via telephone or using an online communication platform such as Microsoft Teams. The interview will be conducted as soon as possible after the event, consent will be obtained by the research fellow prior to starting the interview.

Emergency medicine staff:

For patients suffering cardiac arrest and transferred to hospital, a hospital research nurse / local CRN nurse will contact the relevant ED the same day or the next morning to identify the member(s) of staff most involved with providing care and pass the details onto the ED PI (or their delegate) who will invite them via their work email to participate in the study. The email invitation to participate will include information about the study and a copy of the consent form. ED staff interested in the study will be asked to contact the research team to discuss the study and arrange an interview. Verbal consent to retain contact details will be confirmed when an interview is scheduled. A study information sheet will be posted/emailed to the participant prior to the interview. Formal consent will be obtained on the day of the interview before the interview starts. Consent will be written where interviews are face to face, and audio-recorded where held remotely via telephone or using an online communication platform such as Microsoft Teams. The interview will be conducted as soon as possible after the event, consent will be obtained by the research fellow prior to starting the interview.

Survivors of cardiac arrest / relatives of non-survivors:

We have experience of approaching patients and next of kin following life threatening events in our previous work (ICU decision-making,<sup>70</sup> PARAMEDIC2<sup>69</sup> and in our development of a core outcome set for cardiac arrest).<sup>71</sup> For this study we worked closely with our PPI panel to develop the most appropriate approach to recruitment of patients and relatives, including relatives of non survivors. There is evidence that survivors of cardiac arrest and their relatives suffer significant psychological sequelae including post-traumatic stress disorder,<sup>72,73</sup> with up to 50% of patients having persistent symptoms three months after the event.<sup>74</sup> We therefore do not plan to approach survivors or relatives until at least three months post cardiac arrest (or 3 months post death for relatives of non survivors).

For all cases where ROLE was performed on scene the research paramedic in the relevant ambulance trust will know that the patient has died. In all other cases the research paramedic will not know if the patient survived or died and so will refer to the Summary Care Record at three months post event. The research paramedic will pass this information to the Ambulance Service PI (or their delegate).

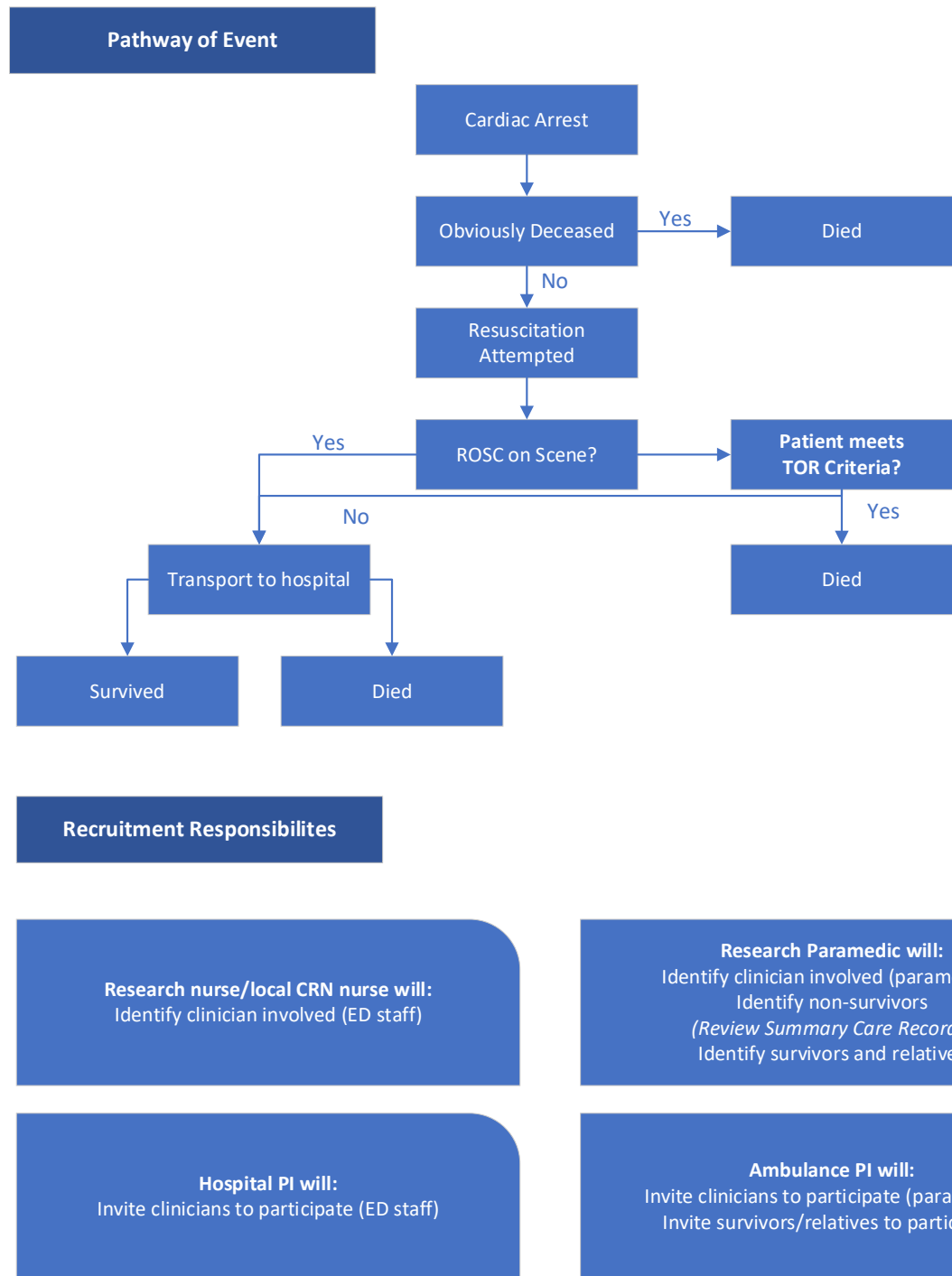
The Ambulance Service PI (of their delegate) will write to survivors and relatives of non survivors with very brief information about the study asking if they (or a family member) would be prepared to take part in the study. Those interested in the study will be asked to contact the research team who will arrange a telephone conversation with the researcher. The researcher will discuss the study in more detail answering any questions raised by the potential participant. Where the participant confirms they are willing to be interviewed verbal consent to retain contact details will be confirmed and an interview scheduled at a mutually convenient time and location. Prior to the interview a more detailed information sheet will be posted/emailed to the participant. Formal consent will be obtained on the day of the interview before the interview starts. Consent will be written where interviews are face to face, and audio-recorded where held remotely via telephone or using an online communication platform such as Microsoft Teams.

If the survivor agrees we will also invite a family member to be interviewed. If the survivor lacks capacity to consent their next of kin will be provided with information about the study and asked if they will agree to be interviewed. In this situation we will ask the next of kin to sign a personal



consent form confirming that they agree that the person would not object to their relative discussing their care with the researcher for the purpose of the study. Consent will be taken immediately prior to the interview. Consent will be written where interviews are face to face, and audio-recorded where held remotely via telephone or using an online communication platform such as Microsoft Teams.

**Figure 2: Recruitment of Participants**



We aim to recruit the paramedics, ED staff and survivors/relatives involved in the same cardiac arrest event to allow comparison of differing perspectives of the event. However, this will not always be possible. Based on our previous experience we expect to find recruitment of survivors/relatives difficult, but that the data from those who do agree to be interviewed will be of great value to the study. If we fail to recruit patients/relatives of non-survivors, we will seek lay participants with a personal interest in heart disease by advertising through national and regional organisations, such as the British Heart Foundation, who support people affected by conditions that increase risk of cardiac arrest and peer support groups for survivors of cardiac arrest e.g. Sudden Cardiac Arrest UK. We will create a sampling frame using characteristics (age group, gender, experience of cardiac arrest) of those who express an interest in participating. For participating Acute Trusts who run a post discharge ICU clinic for patients and their families, the Trust research nurse will identify any patients attending the clinic who have survived a cardiac arrest and provide them with information about the study and contact details for the study team if they wish to learn more or participate.

Recruitment will continue until we reach data saturation. We anticipate interviewing a maximum of 60 clinical staff (30 ambulance staff and 30 ED staff) and approximately 15 patient/family participants with direct experience of the cardiac arrest event and approximately 5 family members who are not present.

The number of cardiac arrest events may be greater than 30 as not all participants will be involved in any one event.

*Withdrawals and exclusions:* Participants can withdraw from the study up to 14 days after their interview without prejudice. After this, the data will be undergoing analysis and it will not be possible to isolate and withdraw particular participant data.

Participants will be given contact details for the researcher who they may contact at any time after they have been recruited, until 14 days after their interview, to inform the team that they wish to withdraw consent. Their wishes will be recorded in the Study Master File using their study ID only and their data removed from the study. The researchers and the co-applicants responsible for WP4 will discuss the situation and decide whether an additional participant at that site or another site should be included. This decision will be informed by various factors including the stage of data collection at the site and the impact of the loss of data on the findings.

## **6.2 Data collection for WP4**

*Data collection:* Interviews will be similarly structured, but modified by stakeholder panels, to address:

- The experience of the cardiac event - what happened, where, when, who was there, what they did, what happened afterwards
- Their reflections on the event – expectations, dilemmas, challenges, values and beliefs
- What would they want others to learn from the event?
- Exploration of attitudes, beliefs and preferences about cardiac arrest more generally, prompted by vignettes developed with input from our expert advisory group and PPI advisory group.

Interviews with family members who were not present will cover the same topics and we will ask them about the source of what they know about the event. Interviews will be carried out face to face or remotely, if preferred by the participant or necessary due to COVID-19 restrictions. To ensure that confidentiality is maintained, face to face interviews will be held at a mutually agreed, suitable location. Remote interviews will be carried out via telephone or using an online communication platform, such as Microsoft Teams, at a mutually agreed time. Informed consent will be obtained prior to interview. Consent will be written where interviews are face to face and audio-recorded where held remotely via telephone or using an online communication platform such as Microsoft Teams. Interviews will usually last for clinicians, up to 40 minutes and for survivor/relatives, up to an hour. Interviews will be transcribed verbatim, transcripts checked and imported into NVivo.

All participants will be offered a shopping voucher (LOVE2SHOP) worth £40, in consideration of their time to take part in the interview.

### **6.3 Data management for WP4**

Personal data will only be held following verbal consent and kept in order to facilitate the arrangement of the interviews. The data will be kept on password control encrypted spreadsheets and stored in a secure area of the computer with access restricted to staff working on the study.

Audio recordings will be transcribed and anonymised. All qualitative data will be uploaded into appropriate software which will be used to assist data management. Audio recordings will be transferred from site to the University securely using encryption either on the audio recorder, or by downloading the recording to an encrypted laptop. The recordings will be transferred to secure university servers for secure storage and copies on the audio recorder and/or laptop deleted. Transfer to any transcription services will be done via a secure system and according to Warwick data transfer SOPs and a contract with a UoW approved transcription service provider. Hand written field notes will be kept in a locked filing cabinet. Field notes recorded electronically will be on an encrypted laptop while the researcher is at the site and then uploaded to secure university servers when they return to the office.

### **6.4 Data analysis for WP4**

*Data quality checks:* all qualitative transcriptions will be checked against the initial interview recording to ensure consistency. A record of these checks will be logged and reported back to the SMG. SMGs will also evaluate interpretations made from the data.

*Data analysis:* Analysis will be undertaken as follows:

- *Comparative analysis of data related to cardiac events*<sup>75</sup> - Data about any one event will be grouped (although sometimes we may only have one data source for an event). From analysis of initial data we will develop an event pathway. This is likely to be before event, arrival at event, assessment, active treatment, evolving the decision to terminate or not, transport, ED activity, post ED. Data will be coded to stages in the pathway. To understand the diversity of experience and the reasons for this diversity, we will compare data from different stakeholders about the same event at the different stages and between events.
- *Thematic analysis*<sup>76</sup> This analysis will focus on data on expectations, dilemmas, challenges, values, attitudes, beliefs and preferences wherever it occurs in the data. Transcripts will be coded close to

text, with codes summarising the coded text. Codes will then be sorted and categorised into themes to provide a rich description of the range of perspectives and how these influence decisions and actions at cardiac events.

- *Descriptive ethical analysis*<sup>77</sup> This involves interpreting and evaluating the ethical or moral dimensions of the reality reported in the interviews. Working with our ethicist we will re-read interview transcripts looking for explicit and implicit ethical concerns for those encountering cardiac arrest in their work/life and the values they express or imply related to cardiac arrest. During analysis we will relate these to current ethical, legal and professional frameworks.

Each analysis will result in a report to inform the normative ethics review and consensus conference.

*Normative ethical analysis:* Findings from all work packages will be considered together with other relevant literature both empirical and theoretical on decision-making around termination of resuscitation, ethical theory and current regulatory frameworks. We will use the process of bioethical enquiry known as reflexive balancing to analyse the normative question of when should resuscitation attempts be terminated and what rules should govern these decisions. This entails identifying and then balancing as far as possible, the range of relevant concerns, interests and priorities that operate on an ethical problem and suggest a coherent compromise.<sup>78</sup> A report of this analysis will feed into the consensus conference discussions.

## **6.5 Outputs for WP4**

*Output:* Reports will be drafted and discussed at a consensus workshop (WP5).

# **7. CONSENSUS CONFERENCE (WP5)**

*Aim:* Develop a national consensus for the optimal approach resuscitation decisions of out of hospital cardiac arrest, by ambulance services.

*Objectives:*

- Present a synthesis of the evidence from previous work packages
- Use a Nominal Group Technique (NGT) to identify, prioritise and achieve consensus on issues around which there is uncertainty or a balancing of risks and benefits
- Produce an updated TOR rule and implementation guidance
- Identify priorities for future research

*Plan:* Data from all previous work packages will be brought together and presented to stakeholders at a national consensus conference to develop a new national TOR guideline for paramedics.

We have experience of running consensus conferences using nominal group technique (NGT)<sup>79</sup> and on sensitive and ethically charged topics.<sup>40</sup>

In advance of the consensus conference the research team, PPI and expert advisory group including members of Joint Royal College Ambulance Liaison Committee (JRCALC) will meet to review all work

package reports and develop a draft TOR rule where options are suggested where evidence is uncertain or there is balancing of risks and benefits.

Stakeholders will be identified with the help of our PPI and expert advisory group including members of JRCALC. We will aim for representatives of organisations speaking on behalf of patients, relatives, paramedics, emergency medicine doctors and nurses, managers of ambulance service and hospitals, civil society groups with an interest in the topic area and/or ethics and values including religious groups and other professional groups with an interest (coroners, police, undertakers). To identify relevant participants, we will contact organisations such as UK ambulance services, NHS England, JRCALC, Association of Ambulance Chief Executives, National Association of Ambulance Medical Directors, College of Paramedics, Resuscitation Council UK, British Heart Foundation, Age UK and other relevant national advocacy groups and charities, groups such as relevant study groups of University of the Third Age and similar organisations and national and regional religious leaders. In addition to the research team, PPI and expert advisory panels, we expect to attract 60 people to the conference with a numerical balance between health professionals and non-health professionals. Those representing charities along with PPI representatives will be reimbursed for time and expenses.

Conference participants will receive in advance, reports from all work packages, the draft termination of rule and details of the purpose and programme of the conference. The conference will be organised as follows. Presentations from Professor Laurie Morrison, an international expert and formal collaborator on this project will be followed by mini-presentations of work package results and the draft termination of resuscitation guideline. The participants will then work in small groups with balanced membership before returning to plenary for final agreement on the TOR guidelines. In small groups participants will identify where there is agreement about the TOR rule and where there is not, where necessary using NGT to prioritise topics for further consideration in plenary. In the plenary the results of the small group work will be presented for discussion. We will use NGT to reach consensus on issues where there remains a lack of consensus within or between small groups. Finally, we will brainstorm on barriers and facilitators to implementation. We will take detailed notes of all discussions during the conference and record all NGT processes. During the meeting we will explore the need for further research and if relevant produce a prioritised list for future research needs.

After the conference we will review conference notes and records to check process and interpretation. Any problems identified will be resolved through email contact with participants. Guided by implementation frameworks such as Normalisation Process Theory<sup>80</sup> we will analyse notes on barriers and facilitators to implementation and develop implementation guidance.

*Output:* Report summarising previous work packages; report of consensus conference; a new TOR guideline and implementation guidance.

## **8. ADVERSE EVENT MANAGEMENT**

We do not expect any adverse or serious adverse events for this study. Should any distress be identified during the interviews, participants will be signposted to appropriate support services (see 9.2 – ‘Disclosure of confidential information’).

## 9. DATA MANAGEMENT

Personal data collected during the study will be handled and stored in accordance with the 2018 Data Protection Act.

### 9.1 Data collection and management

Several modalities will be used for the collection of research data across the different WP (table 2). Full information is provided in the detailed description covering each WP in sections: 3 (WP1), 4 (WP2), 5 (WP3), 6 (WP4) and 7 (WP5).

*Table 2 - Summaries of the main approaches by each work package*

	Systematic Review & meta- analysis	Interviews	Review of local policies and guidelines	Modelling	Consensus Group
WP1	X				
WP2			X		
WP3				X	
WP4		X			
WP5					X

Confidentiality: Any researcher(s) from the study research team needing access to patient records to support the data collection at sites will apply for a research passport/letter of access. When reporting the findings of the study, participants who consent will be assigned a unique participant identification number. All results and findings reported will be anonymised, to ensure no individuals can be identified. Participating hospitals' identities will only be reported with their agreement and specific data relating to each hospital will be reported anonymously using a case identifier.

### 9.2 Data Management

Data collected during the study will be handled and stored in accordance with Warwick Standard Operating Procedures and in compliance with all applicable UK legislation-Further details are documented in section 6 (WP4).

Data collected from the OHCAO registry will be anonymised at a patient level and transferred internally securely.

#### ***Disclosure of confidential information***

If participants show signs of distress we will discuss options for support available to the participant.

If concern arises about unethical or unsafe clinical practice the researcher will consult the WP leads (FG or AS) who, in consultation with the CI (GP), will decide if it is necessary to initiate actions through normal professional channels, which is likely to be through the relevant NHS Trust. We think it is unlikely that serious unprofessional conduct will be observed or disclosed in this study. If any disclosures are made the participant involved in the interview where this practice was revealed (clinician or family member) will be informed that this is happening. The need for a researcher to disclose any evidence of serious

unprofessional conduct will be made clear in the relevant participant information sheets. If the participant agrees we will disclose their contact details to the relevant support services. The University of Warwick (UoW) has a standard operating procedure for responding to disclosures of this nature by research participants.

As with survivors and families of non survivors, if ambulance staff or hospital staff will benefit from access to support services, we will direct them to support services within their relevant Trust.

### **9.3 Database**

No formal databases will be required for this study.

### **9.4 Data storage**

All essential documentation and study records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Any paper forms, meeting notes or other documents will be stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data will be stored in a secure area of the computer with access restricted to staff working on the study.

### **9.5 Data access and quality assurance**

Study participants will be assigned a unique study identifier. Each site will maintain a confidential and secure list of patient identifiable information (name, date of birth, identification number) for the purposes of audit/quality assurance.

Following inclusion of their data in the analysis, the personal identifiable information records for that participant will be destroyed according to Warwick or local site SOPs, once the interviews have been completed for that site. The CI and the WCTU study team (or delegate) will have access to the final study data set from all five work packages. Access requests from both co-investigators and external parties will be considered by the SSC. A formal process will be developed by the study team to facilitate such requests and decisions. Any data shared will be anonymised and transferred as per Warwick SOPs with data sharing agreements in place.

### **9.6 Archiving**

Study documentation and data will be archived for at least ten years after completion of the study at both WCTU and research sites.

### **9.7 End of Study**

The study will officially end on the last day of funding although dissemination of results will continue beyond that date.

Since this study is not implementing any intervention, it is unlikely to be stopped prematurely, unless funding is ended early. If several or all of the research sites withdraw in WP4 during data collection this could result in these aspects of the study ending prematurely or being partially completed.

The Research Ethics Committee will be notified in writing within 90 days when the study has been concluded or within 15 days if terminated early.



## **10. STUDY ORGANISATION AND OVERSIGHT**

### **10.1 Sponsor and governance arrangements**

University of Birmingham NHS Foundation Trust will manage the financial aspects of the grant and has delegated management of the conduct of the study to the University of Warwick. All required ethical approval(s) for the study will be sought using the Integrated Research Application System. The study will be conducted in accordance with all relevant regulations.

Before enrolling patients into the study, each site must ensure that the local conduct of the study has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the study until written confirmation of R&D agreement is received by the PROTECTeD Warwick Clinical Trials Unit team.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. The REC will be notified of the end of the study (whether at planned time or prematurely).

The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the study.

### **10.2 Peer Review**

This proposal has been subject to robust peer review during two rounds of assessment with the NIHR. This process has included evaluation of scientific merit, methodologic, statistical and health economic approaches. It has additionally been assessed by lay reviewers and the NIHR board. We believe this proposal meets the standards of high quality peer review required by the NIHR CRN for adoption to their portfolio. That is, peer review was:

- a) Independent: At least two individual experts reviewed the study
- b) Expert: Reviewers have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study
- c) Proportionate: Peer review should be commensurate with the size and complexity of the study. Large multicentre studies should have higher level (more reviewers with broader expertise and often independent review committee or board), and potentially international peer review

### **10.3 Study Registration**

The study will be eligible for inclusion on the CRN Portfolio. The systematic review (WP1) has been registered on PROSPERO (CRD42019131010).

### **10.4 Notification of serious breaches to GCP and/or study protocol**

A breach which is likely to effect to a significant degree:

- a) The safety or physical or mental integrity of the subjects of the study; or
- b) The scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The sponsor of a clinical study will notify the authorities in writing of any serious breach of:

- a) The conditions and principles of GCP in connection with that study; or
- b) The protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach

#### **10.5 Indemnity**

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

#### **10.6 Study timetable and milestones**

The study will start on the 1<sup>st</sup> June, 2019 and end on the 31<sup>st</sup> May, 2022. See Figure 3 Project Management Plan. We will provide progress reports after each six month period, which will report against the following milestones:

- Months 1-3: Confirmation of research sites, study documents, ethics and governance approvals, contracts and staffing
- Months 1-12: Complete systematic review (WP1)
- Months 6-12: Complete review of ambulance service TOR policy and local practices (WP2)
- Months 12-24: Modelling of alternative TOR rules (WP3)
- Months 7-30: Undertake interviews with ambulance staff, emergency department staff and survivors/relatives of non-survivors of cardiac arrest (WP4)
- Months 34: Consensus conference (WP5)
- Months 30-36: Draft final report

#### **10.7 Administration**

The study co-ordination will be based at WMS/WCTU, University of Warwick.

#### **10.8 Study Management Group (SMG)**

The Study Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the study, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Study Steering Committee or Investigators, as appropriate.

#### **10.9 Study Steering Committee (SSC)**

The study will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The SSC will have an independent Chairperson. Face to face meetings

will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the study will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the study
- Reviewing relevant information from other sources
- Informing and advising on all aspects of the study

The membership of the SSC is shown on page 6.

Meetings will be held at regular intervals determined by need but not less than once a year. Routine business will be conducted by email.

The full remit and responsibilities of the SSC will be documented in the Committee Charter which will be signed by all members.

#### **10.10 Expert Advisory Group (EAG)**

The study will be informed by an expert advisory group (EAG) comprising key stakeholders who will guide the research team and help develop the new guideline. The EAG will:

- support the research team to interpret findings from work packages
- help formulate recommendations
- advise on the content and delivery of outcomes to professional audiences

The expert advisory panel will comprise representatives from JRCALC Clinical Practice Guidelines Development Committee, Association of Ambulance Service Chief Executives (AACE), National Ambulance Service Medical Directors group, College of Paramedics, Royal College of Nursing, National Ambulance Service Cardiac Care Leads Group, Resuscitation Council UK, Faculty of Prehospital Care (Royal College of Surgeons Edinburgh), Royal College of Emergency Medicine and the Royal College of Anaesthetists. To ensure the patient focus is not lost, our PPI co-applicant Mr John Long will also be a member of the EAG. Membership of the EAG is shown on page 6.

Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business will be conducted by email, post or teleconferencing.

#### **10.11 Data Monitoring Committee (DMC)**

Since there is no intervention delivered as part of the study a DMC is not required. We are also using a significant proportion of routinely collected data (WP3), so issues of safety should have been addressed by organisations collecting data as part of their audit processes.

#### **10.12 Essential Documentation**

A Study Master File will be set up according to Warwick SOPs and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the study.

#### **10.13 Financial Support**

This study is funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research (HS&DR) programme (Grant Reference Number 17/99/34). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

MILESTONES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	
Project Month	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	
Set up																																					
Milestone 1 (contracts and staffing)	x		x	x		x																															
Milestone 2 (ethics approval)																																					
Milestone 3 (governance)																																					
Milestone 4 (study documentation)	x		x	x		x																															
Systematic Review and meta analysis																																					
Milestone 5 (draft and run search)																																					
Milestone 6 (first pass review of titles - 2)																																					
Milestone 7 (confirmation of included studies)																																					
Milestone 8 (critical appraisal of included studies)																																					
Milestone 9 (data extraction by reviewer)																																					
Milestone 10 (verification of extracted data)																																					
Milestone 11 (meta analysis)																																					
Milestone 12 (draft paper for submission)																																					
Milestone 13 (1st draft chapter for final manuscript)																																					
Survey of Ambulance Service practices																																					
Milestone 14 (request documentation)																																					
Milestone 15 (review documentation)																																					
Milestone 16 (tabulate findings)																																					
Milestone 17 (identify areas of ambulance service)																																					
Milestone 18 (key staff questionnaire)																																					
Milestone 19 (key staff interview)																																					
Milestone 20 (draft paper for submission)																																					
Milestone 21 (1st draft chapter for final manuscript)																																					
Modelling																																					
Milestone 22 (model ROLE using OH-CAO database)																																					
Milestone 23 (model compliance with TOR rules)																																					
Milestone 24 (model alternate TOR rules)																																				</	

## **11. MONITORING, AUDIT AND INSPECTION**

A Study Monitoring Plan will be developed and agreed by the Study Management Group (SMG) and SSC based on the study risk assessment. The full monitoring plan can be accessed in the study electronic master site file (eSMF) or study master file (SMF). Details of particular importance to note include:

All research team staff from the co-ordinating centre and the research team at the study sites involved in data collecting for WP2 and WP4 will receive appropriate training proportionate to their role. The co-ordinating team will seek confirmation of this training from sites where applicable. CVs will be obtained for site PIs.

Interviews will be conducted by appointed researcher(s) who will have relevant experience and/or training in interviewing patients or families experiencing distressing situations. Consent procedures, interview schedules and interview questions will be developed and reviewed by researchers and co-applicants responsible for the work package, ensuring a consistent but flexible approach that is required for this type of data collection.

Data quality checks will have been completed by the OHCAO registry (WP3), according to their protocols, prior to transfer of the clean anonymised data set to the PROTECTeD study team for analysis. Study documentation and processes will be audited by the Warwick Clinical Trial Unit's Quality Assurance team.

## **12. PATIENT AND PUBLIC INVOLVEMENT (PPI)**

Patient and public involvement is embedded throughout this research. Our co-applicant Mr John Long, has been involved since the inception of this proposal and will be a core member of the research team, contributing to all aspects of the study. We have presented our proposal to the Clinical Research Ambassador Group (CRAG) at Heart of England NHS Foundation Trust and amended our study in line with their recommendations. We also presented our proposal to Redditch and Hale Hearties, a community support group for patients, family, carers and friends of those with heart disease. They were supportive of our plans, felt the composition of the research team was appropriate. The group felt this was an important question and were keen to maintain involvement if the project is funded. Mindful of advice from the PPI panel we have changed the title from the original application (Termination of Resuscitation by Paramedics) to one which sets the study in the context of the wider area of resuscitation decisions in out of hospital cardiac arrest.

At the outset of the project, we will convene a PPI advisory panel to advise on study design, materials and conduct, comment and advise the team on findings, help formulate recommendations and advise on the content and delivery of outcomes to lay audiences. In particular, the PPI panel will advise on approaches to consent and development of areas for interview in WP4 and ensure robust patient and public stakeholder representation at the consensus conference (WP5). In addition our PPI co-applicant (JL) will also sit on our expert advisory panel to ensure PPI input is included and not lost among clinically focused outcomes.

A PPI advisory panel is proposed to advise on study design, materials and conduct, comment and advise the team on findings, help formulate recommendations and advise on the content and delivery of outcomes to lay audiences. The PPI panel will comprise Mr John Long and up to seven other members. We will endeavour to ensure as far as is practicable that there is a balance of members with respect to gender and as far as possible, of age group.

The University of Warwick has well established links with individuals who are keen to provide input into research undertaken at Warwick. In the first instance, we will invite individuals with an interest in cardiac arrest related research, who have worked with us on previous cardiac arrest related research. If too few individuals volunteer, we will extend the invitation to members of CRAG and Redditch and Hale Hearties support group, some of whom have already expressed an interest in working with us.

Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business will be conducted by email, post or teleconferencing.

### **13. DISSEMINATION AND PUBLICATION**

It is anticipated that this study will produce the following outputs:

- An NIHR Monograph which provides an overarching description of the work undertaken
- A new termination of resuscitation guideline, implementation guidance and supporting materials
- Conference presentation at UK, European and international ambulance and resuscitation meetings
- Publications in peer reviewed journals
- Lay summary of research findings

Our dissemination strategy will aim to increase awareness of our findings, stimulate improvements in pre-hospital resuscitation, provide an evidence base for future research funding and promote public engagement and understanding of the research. It will target the following groups:

- 1) Policy makers and commissioners
- 2) Regional Cardiac Networks
- 3) Ambulance services
- 4) Health care providers
- 5) Academic audiences
- 6) Patients and the public
- 7) Resuscitation charities and advocacy groups

We will ensure our patient and public contributors are involved in developing and implementing our dissemination plan. Their focus on improving care for victims of cardiac arrest gives them an insight which complements the experiences of clinical and academic co-applicants. We have strong links with guideline development groups and our previous research has influenced a number of national and international guidelines. We will also harness the contacts and professional networks of members of

our expert advisory group, which contain key opinion leaders in resuscitation and prehospital care. This will ensure results are promulgated across all regional and national resuscitation related networks and to the highest policy making levels, to facilitate adoption of the completed work.

We have considered specific barriers to implementation using the framework developed by Fischer et al.<sup>81</sup> Specific interventions to facilitate adoption include:

- Co-production of the guideline with the key stakeholders as outlined in WP 5.
- Developing a clear, accessible, generalizable evidence based guideline that is relevant to ambulance staff and acceptable to patients and their relatives.
- Working with the ambulance cardiac leads network as key opinion leaders and champions for the new guideline.
- Seeking endorsement of the guideline from key stakeholders.
- Developing an implementation guide and supporting materials (e.g. Continuous Professional Development).
- Audit and incorporate feedback into the national out of hospital cardiac arrest registry annual reports.
- Promoting public engagement throughout the project and sharing a plain language summaries of our findings to patient and public representative organisations, including cardiac care advocacy groups.
- Creation of an evidence base through scientific papers published in high profile and speciality specific journals that provide open access and are widely read by the pre-hospital care, resuscitation, clinical and research communities.
- Presentation of findings at relevant national and international academic conferences. We will also develop supporting material to assist dissemination at professional meetings.
- Publicising key scientific outputs by issuing press releases to established media contacts, making research team members available for interview and using our website, blog, Facebook page and Twitter feed.

We have the support of the guideline development team and expect that the new guideline generated through this research will replace the existing JRCALC ROLE guideline used by ambulance staff. The new guideline will assist prehospital clinicians, when making decisions concerning out of hospital cardiac arrest, optimise outcomes for patients, align care pathways with patient values and reduce demand on NHS services. This work will have national impact soon after study completion.

We have carefully considered the potential barriers to implementation using the framework developed by Fisher et al.<sup>81</sup> Potential barriers include personal factors (ambulance staff knowledge, attitudes and beliefs), guideline factors (lack of evidence, complexity, clarity, layout) and external factors (organizational constraint, resources, lack of collaboration, social and clinical norms). Our dissemination strategy seeks to limit the effect of these barriers through key opinion leaders, providing an evidence base for the guideline, involving patients and public so the recommendations are sensitive to their needs and views, development of continuous professional development packages for ambulance staff, working with the key stakeholder organisations.

Our research will support the implementation of an evidence-based termination of resuscitation guideline for paramedics employed by NHS ambulance services. It will improve healthcare quality for



patients experiencing out-of-hospital cardiac arrest and their families by engaging clinicians, patients, ambulance services and policy makers to provide better care, by reducing variation in practice and optimising the use of limited health resources.

*Author and collaborator contributions*

We will follow the guidance on authorship and contributorship outlined by the ICMJE and the Warwick SOP on publication. This will ensure that all those that make a wholehearted contribution to this project and agree to be included, are named appropriately included in study outputs.

## 14. REFERENCES

1. Hawkes C, Booth S, Ji C, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation* 2017;110:133-40.
2. Committee JRCAL. UK ambulance services clinical practice guidelines 2016: Class Publishing; 2016.
3. Skrifvars MB, Vayrynen T, Kuusma M, et al. Comparison of Helsinki and European Resuscitation Council "do not attempt to resuscitate" guidelines, and a termination of resuscitation clinical prediction rule for out-of-hospital cardiac arrest patients found in asystole or pulseless electrical activity. *Resuscitation* 2010;81:679-84.
4. Nolan JP, Ferrando P, Soar J, et al. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. *Crit Care* 2016;20:219.
5. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC, Callaway CW. Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest: Implications for Prolonging or Terminating Resuscitation. *Circulation* 2016;134:2084-94.
6. Nagao K, Nonogi H, Yonemoto N, et al. Duration of Prehospital Resuscitation Efforts After Out-of-Hospital Cardiac Arrest. *Circulation* 2016;133:1386-96.
7. Matsuyama T, Kitamura T, Kiyohara K, et al. Impact of cardiopulmonary resuscitation duration on neurologically favourable outcome after out-of-hospital cardiac arrest: A population-based study in Japan. *Resuscitation* 2017;113:1-7.
8. Petrie DA, De Maio V, Stiell IG, Dreyer J, Martin M, O'Brien J A. Factors affecting survival after prehospital asystolic cardiac arrest in a Basic Life Support-Defibrillation system. *Cjem* 2001;3:186-92.
9. Morrison LJ, Visentin LM, Kiss A, et al. Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. *N Engl J Med* 2006;355:478-87.
10. Morrison LJ, Verbeek PR, Vermeulen MJ, et al. Derivation and evaluation of a termination of resuscitation clinical prediction rule for advanced life support providers. *Resuscitation* 2007;74:266-75.
11. Morrison LJ, Verbeek PR, Zhan C, Kiss A, Allan KS. Validation of a universal prehospital termination of resuscitation clinical prediction rule for advanced and basic life support providers. *Resuscitation* 2009;80:324-8.
12. Marsden AK, Ng GA, Dalziel K, Cobbe SM. When is it futile for ambulance personnel to initiate cardiopulmonary resuscitation? *BMJ* 1995;311:49-51.
13. Goto Y, Funada A, Nakatsu-Goto Y. Neurological outcomes in children dead on hospital arrival. *Critical Care* 2015;19.
14. Bonnin M, Pepe P, Clark P. Key role of prehospital resuscitation in survival from out-of-hospital cardiac arrest. *Ann Emerg Med* 1990;19:466.
15. Baskett PJ, Steen PA, Bossaert L. European Resuscitation Council Guidelines for Resuscitation 2005: Section 8. The ethics of resuscitation and end-of-life decisions. *Resuscitation* 2005;67:S171-S80.
16. Ruygrok ML, Byyny RL, Haukoos JS. Validation of 3 termination of resuscitation criteria for good neurologic survival after out-of-hospital cardiac arrest. *Ann Emerg Med* 2009;54:239-47.
17. Bonnin MJ, Pepe PE, Kimball KT, Clark PS, Jr. Distinct criteria for termination of resuscitation in the out-of-hospital setting. *JAMA* 1993;270:1457-62.
18. Drennan IR, Case E, Verbeek PR, et al. A comparison of the universal TOR Guideline to the absence of prehospital ROSC and duration of resuscitation in predicting futility from out-of-hospital cardiac arrest. *Resuscitation* 2017;111:96-102.
19. Kashiura M, Hamabe Y, Akashi A, et al. Applying the termination of resuscitation rules to out-of-hospital cardiac arrests of both cardiac and non-cardiac etiologies: a prospective cohort study. *Crit Care* 2016;20:49.
20. Ong ME, Jaffey J, Stiell I, Nesbitt L. Comparison of termination-of-resuscitation guidelines for basic life support: defibrillator providers in out-of-hospital cardiac arrest. *Ann Emerg Med* 2006;47:337-43.

21. Sasson C, Hegg AJ, Macy M, et al. Prehospital termination of resuscitation in cases of refractory out-of-hospital cardiac arrest. *JAMA* 2008;300:1432-8.
22. Yates EJ, Schmidbauer S, Smyth AM, et al. Out-of-hospital cardiac arrest termination of resuscitation with ongoing CPR: An observational study. *Resuscitation* 2018;130:21-7.
23. Paiva EF, Paxton JH, O'Neil BJ. The use of end-tidal carbon dioxide (ETCO<sub>2</sub>) measurement to guide management of cardiac arrest: A systematic review. *Resuscitation* 2018;123:1-7.
24. Touma O, Davies M. The prognostic value of end tidal carbon dioxide during cardiac arrest: a systematic review. *Resuscitation* 2013;84:1470-9.
25. Soar J, Nolan JP, Bottiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Section 3. Adult advanced life support. *Resuscitation* 2015;95:100-47.
26. Tsou PY, Kurbedin J, Chen YS, et al. Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A systematic review and meta-analysis. *Resuscitation* 2017;114:92-9.
27. Reed MJ, Gibson L, Dewar A, Short S, Black P, Clegg GR. Introduction of paramedic led Echo in Life Support into the pre-hospital environment: The PUCA study. *Resuscitation* 2017;112:65-9.
28. Clattenburg EJ, Wroe P, Brown S, et al. Point-of-care ultrasound use in patients with cardiac arrest is associated prolonged cardiopulmonary resuscitation pauses: a prospective cohort study. *Resuscitation* 2018;122:65-8.
29. Levick N, Li G, Yannaccone J. Biomechanics of the patient compartment of ambulance vehicles under crash conditions: testing countermeasures to mitigate injury. *SAE transactions* 2001;1329-35.
30. Becker LR, Zaloshnja E, Levick N, Li G, Miller TR. Relative risk of injury and death in ambulances and other emergency vehicles. *Accident Analysis & Prevention* 2003;35:941-8.
31. Auerbach PS, Morris JA, Phillips JB, Redlinger SR, Vaughn WK. An analysis of ambulance accidents in Tennessee. *JAMA* 1987;258:1487-90.
32. Fournier M, Chenaitia H, Masson C, Michelet P, Behr M, Auffray J-P. Crew and patient safety in ambulances: results of a personnel survey and experimental side impact crash test. *Prehospital and disaster medicine* 2013;28:370-5.
33. McRoy BS, Lawrence R. How to build the crew chain of safety. Safe driving is a priority for Richmond Ambulance Authority crews. *EMS World* 2014;43:26-8, 30, 2.
34. Smith N. A National Perspective on Ambulance Crashes and Safety. Guidance from the National Highway Traffic Safety Administration on ambulance safety for patients and providers. *EMS World* 2015;44:91-2, 4.
35. Kahn CA, Pirrallo RG, Kuhn EM. CHARACTERISTICS OF FATAL AMBULANCE CRASHES IN THE UNITED STATES: AN 11-YEAR RETROSPECTIVE ANALYSIS. *Prehospital emergency care* 2001;5:261-9.
36. Lutman D, Montgomery M, Ramnarayan P, Petros A. Ambulance and aeromedical accident rates during emergency retrieval in Great Britain. *Emergency medicine journal* 2008;25:301-2.
37. Olasveengen TM, Wik L, Steen PA. Quality of cardiopulmonary resuscitation before and during transport in out-of-hospital cardiac arrest. *Resuscitation* 2008;76:185-90.
38. Lyon RM, Crawford A, Crookston C, Short S, Clegg GR. The combined use of mechanical CPR and a carry sheet to maintain quality resuscitation in out-of-hospital cardiac arrest patients during extrication and transport. *Resuscitation* 2015;93:102-6.
39. Lewis LM, Ruoff B, Rush C, Stothert JC, Jr. Is emergency department resuscitation of out-of-hospital cardiac arrest victims who arrive pulseless worthwhile? *American Journal of Emergency Medicine* 1990;8:118-20.
40. Perkins GD, Griffiths F, Slowther A-M, et al. Do-not-attempt-cardiopulmonary-resuscitation decisions: an evidence synthesis. 2016.
41. Cohn S, Fritz Z, Frankau J, Laroche C, Fuld J. Do not attempt cardiopulmonary resuscitation orders in acute medical settings: a qualitative study. *QJM: An International Journal of Medicine* 2013;106:165-77.

42. Curtis JR, Burt RA. Why are critical care clinicians so powerfully distressed by family demands for futile care? *Journal of critical care* 2003;18:22-4.
43. Hick JL, Mahoney BD, Lappe M. Factors influencing hospital transport of patients in continuing cardiac arrest. *Annals of Emergency Medicine* 1998;32:19-25.
44. Anderson NE, Gott M, Slark J. Commence, continue, withhold or terminate?: a systematic review of decision-making in out-of-hospital cardiac arrest. *European Journal of Emergency Medicine* 2017;24:80-6.
45. Mao DRH, Ong MEH, Bang CL, Salim MDT, Ng YY, Lie DA. Psychological Comfort of Paramedics with Field Death Pronouncement: A National Asian Study to Prepare Paramedics for Field Termination of Resuscitation. *Prehospital Emergency Care* 2018;22:260-5.
46. Grudzen CR, Timmermans S, Koenig WJ, et al. Paramedic and emergency medical technicians views on opportunities and challenges when forgoing and halting resuscitation in the field. *Academic Emergency Medicine* 2009;16:532-8.
47. Mikkelsen S, Schaffalitzky de Muckadell C, Binderup LG, Lossius HM, Toft P, Lassen AT. Termination of prehospital resuscitative efforts: a study of documentation on ethical considerations at the scene. *Scand J Trauma Resusc Emerg Med* 2017;25:35.
48. Edwardsen EA, Chiumento S, Davis E. Family perspective of medical care and grief support after field termination by emergency medical services personnel: a preliminary report. *Prehosp Emerg Care* 2002;6:440-4.
49. Delbridge TR, Fosnocht DE, Garrison HG, Auble TE. Field termination of unsuccessful out-of-hospital cardiac arrest resuscitation: acceptance by family members. *Ann Emerg Med* 1996;27:649-54.
50. Hoare S, Morris ZS, Kelly MP, Kuhn I, Barclay S. Do Patients Want to Die at Home? A Systematic Review of the UK Literature, Focused on Missing Preferences for Place of Death. *PLoS One* 2015;10:e0142723.
51. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC, Callaway CW. Association between duration of resuscitation and favorable outcome after out-of-hospital cardiac arrest: Implications for prolonging resuscitation. *Circulation Conference: American Heart Association's* 2016;134.
52. Nagao K, Nonogi H, Yonemoto N, et al. Duration of Prehospital Resuscitation Efforts After Out-of-Hospital Cardiac Arrest. *Circulation* 2016;133:1386-96.
53. Drennan IR, Case E, Verbeek PR, et al. A comparison of the universal TOR Guideline to the absence of prehospital ROSC and duration of resuscitation in predicting futility from out-of-hospital cardiac arrest. *Resuscitation* 2017;111:96-102.
54. Kurz MC, Dante SA, Puckett BJ. Estimating the impact of off-balancing forces upon cardiopulmonary resuscitation during ambulance transport. *Resuscitation* 2012;83:1085-9.
55. Murray B, Kue R. The Use of Emergency Lights and Sirens by Ambulances and Their Effect on Patient Outcomes and Public Safety: A Comprehensive Review of the Literature. *Prehosp Disaster Med* 2017;32:209-16.
56. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* 2018;319:388-96.
57. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
58. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
59. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529-36.
60. Moons KG, Wolff RF, Riley RD, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Annals of internal medicine* 2019;170:W1-W33.

61. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. *International journal of technology assessment in health care* 2013;29:117-22.
62. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 2008;336:924-6.
63. Morrison LJ, Bigham BL, Kiss A, Verbeek PR. Termination of resuscitation: a guide to interpreting the literature. *Resuscitation* 2008;79:387-90.
64. Leeflang M, Deeks J, Gatsonis C, Bossuyt P. Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;149:889-97.
65. Leeflang MM, Deeks JJ, Takwoingi Y, Macaskill P. Cochrane diagnostic test accuracy reviews. *Systematic reviews* 2013;2:1-6.
66. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *Journal of clinical epidemiology* 2005;58:882-93.
67. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on resuscitation (American heart association, European resuscitation Council, Australian and New Zealand Council on resuscitation, heart and stroke Foundation of Canada, InterAmerican heart Foundation, resuscitation Council of southern Africa, resuscitation Council of Asia); and the American heart association emergency cardiovascular care Committee and the Council on cardiopulmonary, critical care, perioperative and resuscitation. *Circulation* 2015;132:1286-300.
68. Perkins GD, Brace-McDonnell SJ. The UK out of hospital cardiac arrest outcome (OHCAO) project. *BMJ Open* 2015;5:e008736.
69. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *New England Journal of Medicine* 2018.
70. Bassford C, Slowther A, Rees K, Krucien N, Fritz Z, Quinton S. Gatekeeping in intensive care: understanding and improving the decision-making process surrounding admission to the intensive care unit. University of Warwick, Coventry, UK 2015.
71. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. *Circulation* 2018;137:e783-e801.
72. Zimmerli M, Tislar K, Balestra G-M, Langewitz W, Marsch S, Hunziker S. Prevalence and risk factors for post-traumatic stress disorder in relatives of out-of-hospital cardiac arrest patients. *Resuscitation* 2014;85:801-8.
73. Presciutti A, Verma J, Pavol M, et al. Posttraumatic stress and depressive symptoms characterize cardiac arrest survivors' perceived recovery at hospital discharge. *General hospital psychiatry* 2018;53:108-13.
74. Viktorisson A, Sunnerhagen KS, Pöder U, Herlitz J, Axelsson ÅB. Well-being among survivors of out-of-hospital cardiac arrest: a cross-sectional retrospective study in Sweden. *BMJ Open* 2018;8:e021729.
75. Miles MB, Huberman AM. *Qualitative data analysis: An expanded sourcebook*: sage; 1994.
76. Boyatzis RE. *Transforming qualitative information: Thematic analysis and code development*: sage; 1998.
77. Dunn M, Sheehan M, Hope T, Parker M. Toward methodological innovation in empirical ethics research. *Cambridge Quarterly of Healthcare Ethics* 2012;21:466-80.
78. Ives J. A method of reflexive balancing in a pragmatic, interdisciplinary and reflexive bioethics. *Bioethics* 2014;28:302-12.
79. Consensus JI, Ellard DR. Intraarticular facet injections for low back pain: design considerations, consensus methodology to develop the protocol for a randomized controlled trial. *Pain Physician* 2015;18:473-93.
80. Murray E, Treweek S, Pope C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med* 2010;8:1-11.

81. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation—a scoping review. Healthcare; 2016: Multidisciplinary Digital Publishing Institute. p. 36.