

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)

PARAMEDIC 2: The Adrenaline Trial

1. Is your project research?

Yes No

2. Select one category from the list below:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

Yes No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

Yes No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA?

Yes No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product?

Yes No

2e. Please answer the following question(s):

- a) Does the study involve the use of any ionising radiation? Yes No
- b) Will you be taking new human tissue samples (or other human biological samples)? Yes No
- c) Will you be using existing human tissue samples (or other human biological samples)? Yes No

3. In which countries of the UK will the research sites be located?(Tick all that apply)

- England
 Scotland
 Wales
 Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- England
 Scotland
 Wales
 Northern Ireland
 This study does not involve the NHS

4. Which review bodies are you applying to?

- NHS/HSC Research and Development offices
 Social Care Research Ethics Committee
 Research Ethics Committee
 Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
 Gene Therapy Advisory Committee (GTAC)
 National Information Governance Board for Health and Social Care (NIGB)
 National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

4a. Will you be seeking data from Hospital Episode Statistics (HES) or the Secondary Uses Service (SUS)?

Yes No

4b. Will you only be seeking non-identifiable HES/SUS data?

Yes No

5. Will any research sites in this study be NHS organisations?

Yes No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

Yes No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

Yes No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.

6. Do you plan to include any participants who are children?

Yes No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

Yes No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

Yes No

9. Is the study or any part of it being undertaken as an educational project?

Yes No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product



Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
PARAMEDIC 2: The Adrenaline Trial

Please complete these details after you have booked the REC application for review.

REC Name:
Oxford C REC

REC Reference Number:
14/SC/0157

Submission date:
07/03/2014

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac arrest

A3-2. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- National coordinating investigator
 Principal investigator

Given name	Gavin
Family name	Perkins
Qualification (MD...)	[REDACTED]
Institution name	University of Warwick
Institution department name	Warwick Clinical Trials Unit
Street address	Gibbet Hill Road
Town/city	Coventry
Post Code	CV4 7AL
Country	UNITED KINGDOM

Date: 07/03/2014
Work E-mail [REDACTED]

* Personal E-mail [REDACTED]
Work Telephone [REDACTED]

147538/575440/1/735

Street address	Gibbet Hill Road	Reference:	IRAS Version 3.5
NHS REC Form	Coventry	14/SC/0157	
Post Code	CV4 7AL		
Country	UNITED KINGDOM		
Work E-mail	[REDACTED]		
* Personal E-mail			
Work Telephone	[REDACTED]		
* Personal Telephone/Mobile			
Fax	[REDACTED]		

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.*

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

	Title Forename/Initials Surname
	[REDACTED] [REDACTED]
Address	Medical School, Gibbet Hill Road Coventry
Post Code	CV4 7AL
E-mail	[REDACTED]
Telephone	
Fax	

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number:

Protocol Version: 1.0

Protocol Date: 07/03/2014

Funder's reference number: 12/127/126

Project website: TBC

Registry reference number(s):

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

European Clinical Trials Database (EudraCT) number: 2014-000792-11

Additional reference number(s):

Ref.Number	Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

Yes No

Please give brief details and reference numbers.
Date: 07/03/2014

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147538/575440/1/735

Yes No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.

A cardiac arrest occurs when the heart suddenly stops beating, and is one of the most severe medical emergencies. Over 50,000 people die each year following an out of hospital cardiac arrest (OHCA) in the UK, less than 10% of patients survive. Although adrenaline has been used to treat cardiac arrest for a number of years, no one is really sure about whether it is safe and effective for improving long-term survival and helping the brain to recover.

The aim of this trial is to work out how safe and effective adrenaline is as a treatment for patients who suffer out of hospital cardiac arrest.

This trial will involve putting people into two groups where one group receive the active drug (adrenaline) and the other group a dummy drug (known as a placebo). The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The study is referred to as a "double blind trial", as neither the patient nor the paramedic / nurse/ doctor will know in which treatment group someone was in.

We will collect data on 8,000 patients who have been treated for cardiac arrest. All surviving patients will be invited to take part in the follow up which involves completing questionnaires about health and quality of life after the cardiac arrest.

A6-2. Summary of main issues. Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

There are a number of important ethical issues to be considered in conducting this trial.

1. The trial involves withholding a drug (adrenaline) that is currently given as part of standard care. Section 1.1 of the protocol summarises the current evidence about the use of adrenaline as a treatment for cardiac arrest. In brief there is some evidence that adrenaline leads to better short-term survival. Whether it improves long-term survival and how it affects brain function after cardiac arrest is uncertain. Whilst some studies suggest it may be beneficial, others suggest it may be ineffective or harmful. The trial has the support of the Resuscitation Council (UK), Association of Ambulance Medical Directors and College of Paramedics (letters of support enclosed). Our survey of UK clinician's views about the effectiveness of adrenaline shows substantial uncertainty amongst the clinical community. A placebo controlled trial is necessary to resolve this uncertainty.

2. Patients will be enrolled in the trial prior to consent being obtained. The occurrence of an out of hospital cardiac arrest is unpredictable. Within seconds of cardiac arrest a person becomes unconscious and thus incapacitated. Treatment must be started immediately in an attempt to save the person's life. Studies suggest that if adrenaline is effective, the earlier it is given the more likely it will be beneficial. In this setting it will not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying emergency treatment. It will not therefore be possible to obtain prospective consent directly from the research participant. We plan to obtain consent from the patient or their legal representative as soon as is practicable once the initial emergency has passed to inform them of their participation and request consent to continue with data collection and follow up. We will ensure that general information about the trial and contact details for further information is freely available in public forums throughout the trial. Systems will be put in place (similar to the established systems for informing ambulance staff about a Do Not Attempt Resuscitation Decision) to allow a patient to decline in advance

participation in the trial in the event that they sustain a cardiac arrest

3. Patients and their next of kin will be informed about the trial when they are particularly vulnerable, either because of their medical condition (patients) or because of extreme distress (relatives). The research team will work closely with the clinical teams caring for the patients to ensure that any approach is made as sensitively as possible and that support is available for patients and families who are distressed. The research paramedics will have training in assessing capacity to consent to research and in speaking to families in emotionally difficult situations.

4. Some participants may lack capacity to consent to continue in the study. The Research Paramedic or hospital team will assess if the patient has capacity to consent. In the event that a patient lacks capacity to consent, the Research Paramedic will work with the hospital team to identify a legal representative.

5. The patient may regain capacity as the study progresses. It is possible that the patient will have regained capacity by the time the 3 month visit is due. When contacting the legal representative to arrange the 3 month visit, we will ask to speak to the patient. If on assessment of the patient either on the phone or on the visit it is found that the patient still lacks capacity the legal representative will be asked to complete the questionnaires on behalf of the patient. If the patient has capacity then information will be provided about the trial and consent sought. Specific guidelines have been written by the trial team if the scenario arises that a legal representative responds on behalf of the patient to an invitation letter by post and wants to take part with postal questionnaires only (i.e capacity cannot be established face to face).

6. The need to inform next of kin of participants who do not survive about the trial. Informing the family about the trial ensures that the process of trial recruitment is open and transparent, and reduces the likelihood that family members discover at a later date that their relative was involved in a trial without their knowledge. However, knowledge of trial participation after the event may also place a significant burden on the next of kin at a time of heightened emotional distress due to the loss of their relative or friend. Any strategy to inform family or next of kin following a patient's death needs to carefully balance the need for transparency with the need to minimise their distress. There are a number of ways in which we could approach informing the relatives of those that do not survive.

a) Passive methods include placing information about the trial in publically accessible places and targeted sites likely to be attended by relatives of the deceased (e.g. in the ambulance, hospitals, GP surgeries, Registrar of Births and Deaths offices). Such information would contain brief details about the study and a contact telephone number and address for further information. An advantage of passive methods is that they allow people to make a choice about whether they wish to seek further information and the timing of that approach. However one cannot be certain that relatives of all participants will see them. Discussion with investigators of previous UK trials (e.g. CRASH trials, Brain injury trials) indicates that passive strategies, although not formally evaluated, have been used successfully.

b) Active strategies involve making direct contact with relatives (e.g. posting or hand-delivering a participant information leaflet, organising for a face to face meeting or telephone call). Concerns about the potential burdens to information recipients and the practicalities of this approach mean that it has not been used in previous UK out of hospital cardiac arrest trials. There are practical barriers to providing information actively. The sudden and unpredicted nature of cardiac arrest mean that the relatives / next of kin may not be identifiable at the time of the cardiac arrest. For people where resuscitation efforts are terminated in the home (approximately 40% of total cases) it is not possible for the paramedic who attends the cardiac arrest to spend the necessary time to explain about the study and answer questions. Given these difficulties with face-to-face consultation an alternative is to send written information by post. We have concerns that this un-solicited approach and absence of an opportunity to ask questions immediately upon receipt could exacerbate an already traumatic and stressful experience. We have carefully considered the benefits and burdens of different approaches to informing the relatives of the deceased about the trial. We have concluded that the passive approach outlined above will minimise distress to relatives while maintaining transparency and openness about participation in the trial. We will monitor how this approach works during the pilot phase of the study and if necessary revise during the progression to the main trial. We have discussed this in detail with our clinical ethicist and patient representatives (comments enclosed) and have their support for this approach. However we would welcome the views of the ethics committee on this difficult question.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. Please tick all that apply:

- Case series/ case note review
- Case control
- Cohort observation
- Controlled trial without randomisation
- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study

- Laboratory study
- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

A8. Type of medicinal trial:

- Clinical trial of an unlicensed investigational medicinal product
- Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- Clinical trial of a licensed medicinal product used according to the SmPC
- Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

- Human pharmacology (Phase I) Yes No
- Therapeutic exploratory trial (Phase II) Yes No
- Therapeutic confirmatory trial (Phase III) Yes No
- Therapeutic use trial (Phase IV) Yes No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To determine the clinical effectiveness of adrenaline in the treatment of out of hospital cardiac arrest, measured as survival to 30 days.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To evaluate the effects of adrenaline on survival and recovery of survivors at 3, 6 and 12 months after the cardiac arrest, and to establish the cost-effectiveness of using adrenaline.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Use of adrenaline in cardiac arrest increases short-term survival (hours) but there remains doubt whether this is translated into increased long-term outcomes (days, months). Observational studies suggest an association between adrenaline and worse long-term survival.

Adrenaline is currently used to treat cardiac arrests, and if harmful, may be responsible for many avoidable deaths. Therefore it is crucial to answer the questions about adrenaline as quickly as possible.

A randomised controlled trial of adrenaline has the support of key stakeholders such as the College of Paramedics, Ambulance Service Medical Directors, Joint Royal College Ambulance Liaison Committee, Resuscitation Council (UK) and patient representatives.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

This trial will involve putting people into two groups where one group receive the active drug (in this case adrenaline) and the other group a dummy drug (known as a placebo). The two groups will have the same number of patients (4,000 in each). The results will be compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The study is referred to as a "double blind trial", as

This trial will involve putting people into two groups where one group receive the active drug (in this case adrenaline) and the other group a dummy drug (known as a placebo). The two groups will have the same number of patients (4,000 in each). The results will be compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The study is referred to as a "double blind trial", as neither the patient nor the paramedic / nurse/ doctor will know which treatment group someone was in.

Whether the patients survive to 30 days and recovery of the patients will be compared in both groups. It is possible to find this data without the patient having to do anything, as long as the patient does not object to us collecting this data from their medical notes and NHS databases.

All patients who survive the cardiac arrest will be contacted by the Research Paramedic in hospital once they are on the ward and the initial emergency has passed. The Research Paramedic will explain the trial and that the patient has been included. The Research Paramedic will answer any initial questions and give the patient an information sheet to read. The Research Paramedic will then go back and check with the patient if they are happy for us to continue to collect data and take part in the follow up. If someone does not have the mental capacity to consent we will inform their next of kin known as the personal legal representative and ask them to consent of their behalf.

If the patient wants to take part in the follow up this will involve completing questionnaires about their quality of life and general health at 3 months and 6 months after the cardiac arrest.

The trial is due to start in September 2014. Data will be monitored regularly and the trial may need to stop if a difference is found. Otherwise data will be collected for 3.5 years and results will be known in 2019.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

Give details of involvement, or if none please justify the absence of involvement.

██████████ is our patient public representative, a former senior police officer with extensive experience of working with charities dedicated to reducing death from cardiac arrest. ██████████ has attended meetings and discussions and has been involved in the production of trial documentation including the protocol, the patient information sheet and consent form. He will attend trial related meetings throughout the trial. We will also include two patient public representatives on the Trial Steering Committee.

A14-2. Have you tested the acceptability of using patient identifiable data in this study without consent?

Please give details.

The PARAMEDIC Trial and OHCAO studies use identifiable data from participants without consent. No complaints or requests for withdrawal of data have been received.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

- 1.Cardiac arrest in out of hospital environment
- 2.Advanced life support initiated and / or continued by ambulance service clinician

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- 1.Known or apparent pregnancy
- 2.Known or apparently aged under 16 years
- 3.Cardiac arrest secondary to anaphylaxis
- 4.Adrenaline given prior to arrival of ambulance service clinician

RESEARCH PROCEDURES, RISKS AND BENEFITS

- 3. Cardiac arrest secondary to anaphylaxis
- 4. Adrenaline given prior to arrival of ambulance service clinician

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Questionnaires: SF12 and EQ-5D administered at 3 and 6 months post cardiac arrest	2	0	15 minutes	Paramedic Research Fellow, home
Questionnaires Mini Mental State Examination (MMSE), Hospital Anxiety and Depression Scale (HADS) Post Traumatic Stress (PTSD) at 3 months post cardiac arrest	1	0	15 minutes	Paramedic Research Fellow, home
Modified Rankin Scale (mRS) hospital discharge, 3 and 6 months	3	0	5 minutes	Paramedic Research Fellow and/or hospital staff, home
Consent patient/ legal representative	1	0	30 minutes	Paramedic Research Fellow, hospital/home
IQCODE and 2 simple questions 3 and 6 months post cardiac arrest	2		5min	Paramedic Research Fellow, home

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Advanced Life Saving Resuscitation	1	1	20minutes	Ambulance Service Staff

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

Yes No

If Yes, please give details, explain the risks and justify the need to withhold the intervention or procedure:

The primary objective of this trial is to determine the clinical effectiveness of adrenaline in the treatment of OHCA. Therefore we are conducting a randomised controlled trial whereby half the patients will receive adrenaline and half will receive a comparator i.e placebo.

A21. How long do you expect each participant to be in the study in total?

Approximately 6% of the patients (surviving the cardiac arrest) will potentially be in the study for 12 months.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Risks and burdens: A fundamental issue in this trial is the question of whether the current evidence on the use of adrenaline in cardiac arrest raises sufficient doubt about its efficacy and concern about its potential harm to justify a trial that involves withholding adrenaline from some participants. Most clinical drug trials involve either the comparison of a new drug with the current best treatment or in cases where no current best treatment exists, with a placebo. This trial is unusual in that the underlying hypothesis is that current best practice may be harmful therefore it is ethically necessary to seek evidence to confirm or refute this hypothesis, and that this evidence can only reliably be obtained by a trial that includes participants who do not receive currently recommended treatment. The aim is not to investigate whether another drug is better than adrenaline but to investigate whether adrenaline is more harmful than no adrenaline. The hypothesis that adrenaline is harmful raises the question of what is meant by harm. As we have outlined in our review of current evidence, there is evidence that adrenaline as currently used improves the rate of return of spontaneous circulation (ROSC). Thus it is possible that some people who are entered into the trial and are randomised to receive placebo may fail to achieve return of spontaneous circulation as a result of participating in the trial. However the available evidence on long-term survival (survival to hospital discharge) suggests that some participants who are randomised to placebo will survive to leave hospital when they would have died if they had received adrenaline; that is they will survive as a result of participating in the trial. So for individual participants there is a risk/benefit trade-off for participation which is uncertain because we cannot know on an individual patient basis which person will benefit from the adrenaline and who will be harmed by it.

The current evidence suggests that more people will be harmed than will benefit (if we consider survival to discharge more beneficial than initial survival followed by early death). However the evidence is not so strong that we can say adrenaline should not be used. As we have shown in our survey of practitioners there is equipoise on this question. Given the uncertainty of the evidence, and the life threatening nature of the condition being treated, it is ethically important that we obtain the best evidence we can to justify treatment, while ensuring that the interests of the research participants remain paramount. In considering the interests of the research participants the question is whether for any individual participant the benefits of participating outweigh the risk of harm, or at least the harm/benefit balance is neutral. Based on current evidence it would seem that risks and benefits from participating in this trial are reasonably balanced (if a participant is randomised to placebo they may have a reduced chance of immediate survival but an increased chance of surviving to leave hospital. Our initial PPI work suggest that members of the public weigh long term survival higher than short term recovery of spontaneous circulation so it would seem reasonable to assume potential participants might agree to taking part if they were able to do so.

Minimising risk

The study will be overseen by a Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) appointed by the National Institute for Health Research Health Technology Assessment Programme Director. The majority of members of the TSC will be independent from the study investigators. All members of the DMC will be independent. The study Chief Investigators and other members of the study team may attend meetings in an advisory capacity at the request of the DMC chair.

The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The Data Monitoring Committee (DMC) will monitor safety in this trial. The outcomes of primary interest are long-term outcomes (30 day survival and neurological status). We will regularly prepare reports for the DMC initially at an interval to be confirmed by that group. The DMC will determine the nature of any early stopping rules. We suggest a differing threshold is adopted for early termination if standard care (adrenaline) is more effective compared to if placebo is more effective. This is based on a combination of minimising any risks to patients whilst producing robust evidence that will change practice. We suggest that the balance of evidence that would be needed to change current standard practice (adrenaline use) to be greater.

Patient and public involvement. Because of the particular ethical difficulty of conducting a trial which involves withholding a standard treatment, and the major life changing impact on participants, it will be imperative to have procedures for close surveillance of trial data. To address these concerns we will include two PPI representatives in

the Trial Steering Committee.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

Yes No

If Yes, please give details of procedures in place to deal with these issues:

Patients and relatives of victims of out of hospital cardiac arrest often suffer from symptoms of anxiety, depression and post traumatic stress disorder for weeks or months after the initial event.

Researchers conducting interviews will be trained on how to recognise and sensitively support patients or their relatives who are distressed during the conduct of interviews / questionnaires. The Researchers will be provided with information about systems available to support them at this difficult time (e.g. <http://www.bereavementadvice.org/useful-contacts/useful-contacts-.php>) and will facilitate contact with professional healthcare services (e.g. general practitioner) if requested

It is not anticipated that criminal or other disclosures requiring action will occur during the study.

A24. What is the potential for benefit to research participants?

There is the potential amongst patients who receive adrenaline that a greater number will have their hearts re-started and will survive in the short term (mins to hours).

The available evidence on long-term survival (survival to hospital discharge) suggests that some participants who are randomised to placebo will survive to leave hospital when they would have died if they had received adrenaline; that is they will survive as a result of participating in the trial. Participants receiving placebo may also avoid the potential side effects of adrenaline (irregular heart beat, adverse effects on metabolics, brain injury).

Participation in the study will provide critical information about the most effective way to resuscitate future patients that sustain an out of hospital cardiac arrest.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.

Not Applicable.

A26. What are the potential risks for the researchers themselves? (if any)

Conducting research in cardiac arrest can be emotionally draining to researchers who are faced daily with stories of sad and tragic deaths of many hundreds of people. It is possible that this exposure may lead to some individuals becoming distressed by such exposure.

Our working systems promote a culture of openness and we encourage discussion and sharing if researchers feel burdened or troubled by participation the study.

The study co-ordinating centre (University of Warwick) and partner Ambulance Trusts have access to trained and experienced counsellors who are accessible through our occupational health departments. The availability of these support services are highlighted during the induction of new staff. Access can be via self referral or supported by the individuals line manager.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will

be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Patients will be enrolled into the trial by the attending paramedic if they meet the eligibility criteria. Identification of each trial patient will be carried out by the participating ambulance services. They will set up their own internal systems for ensuring all trial patients are notified to the trial co-ordinating centre (Warwick Clinical Trials Unit (WCTU) as quickly as possible.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

Yes No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

Yes No

A29. How and by whom will potential participants first be approached?

The first attempt to contact the patient and inform them of their enrolment into the trial will be during their stay in hospital before hospital discharge. We plan to make contact as soon as practically possible after the initial emergency has passed and taking the utmost care and sensitivity in doing so. Following our experience from a 4,400 patient study in out of hospital cardiac arrest (PARAMEDIC trial) and talking to fellow researchers from the REVIVE cardiac arrest study and discussions with patient and public representatives, we believe the earliest practicable time to contact patients and relatives is once the patient is discharged from ICU and is on a hospital ward. This allows sufficient time for the research team to be made aware of enrolment, identify who the patient is, check which hospital the patient was transferred to, whether they are still alive and to verify with the hospital team where the patient is within the hospital. Transfer to a ward will indicate that the initial emergency has passed and the patient's condition will have stabilised. It is also more likely that the patient has regained consciousness and it will avoid any confusion or additional distress of making an approach while the patient remains critically ill in intensive care.

A30-1. Will you obtain informed consent from or on behalf of research participants?

Yes No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

The Research Paramedics will be fully trained on informed consent and assessing capacity, GCP guidelines, relevant legislation and the trial related procedures around consent.

Informed consent will ideally be taken with the patient or their legal representative on the hospital ward, after enrolment into the trial.

The Research Paramedic, or hospital team will assess if the patient has capacity to consent. If the patient has capacity, they will be provided with the information sheet explaining the trial and the options for their involvement. The patient will be allowed time to consider the information provided, have the opportunity to ask questions and discuss with others. The Research Paramedic or hospital team will then ask when the patient would like someone to come back to discuss participation further and potentially take consent.

In exceptional circumstances if we were not able to make contact with the patient during the hospital stay, we will write to the patient. If the patient responds to the invitation letter sent by post and agrees to have a home visit, written consent would be taken at the 3 month visit.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

Yes No

A30-3. Why is it not practicable for either the researcher's organisation, or the current holder of the information required by the researcher, to seek or obtain patient consent for proposed use of patient identifiable information?

The occurrence of an out of hospital cardiac arrest is unpredictable. Within seconds of cardiac arrest a person becomes unconscious and thus incapacitated. It will not therefore be possible to obtain prospective consent directly from the research participant.

In this setting it will not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying emergency treatment.

A31. How long will you allow potential participants to decide whether or not to take part?

As long as they need.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- Yes
 No
 Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

It is unlikely that any participants will already be participating in research studies and paramedics recruiting and treating the patients will have no way of finding out and no time to do this. Participation in research would have no bearing on treatment for out of hospital cardiac arrest.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)

As recruitment will take place in Wales, invitation letters, patient information sheets and consent forms will be translated into Welsh language. We will arrange for back translation to be carried out.

Large-print versions of the trial information and questionnaires will be available if needed.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Invitation letters, patient information sheets and consent forms will be translated into Welsh language. We will arrange for back translation to be carried out.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Trial treatment will last for a short period of time so emergence of new information would not affect the treatment of any individual. New research will be monitored by the research team and included in reports to the Data Monitoring Committee who will advise on continuation of the trial if new evidence emerges from other studies.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
 - Manual files including X-rays
 - NHS computers
 - Home or other personal computers
 - University computers
 - Private company computers
 - Laptop computers

Further details:

Access to medical notes is needed to establish mRS at hospital discharge (small group of patients) either the hospital staff or Research Paramedic will do this.

Personal data is needed to WCTU can log surviving patients on HSCIC to track survival to 12 months and also to co-ordinate the initial contact with patients and to co-ordinate patient follow up visits.

Sharing of personal data will include WCTU seeking data from ambulance services hospitals, HSCIC ICNARC and HES as per relevant approvals.

A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

Data will be identified in the study database by unique trial code (TNO) and identifiable details will only be used where this is necessary i.e to contact patients about their enrolment and follow up.

If identifiable data are transferred outside the clinical trials unit, secure methods such as encryption are always used in accordance with the WCTU's standard operating procedures.

Published data will be anonymised.

A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

Personal data will be accessed initially by the ambulance services and sent to WCTU for surviving patients (small proportion of patients) so that the WCTU can track survival to 12 months and to co-ordinate contact with patients about their enrolment.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

- Less than 3 months
- 3 – 6 months
- 6 – 12 months
- 12 months – 3 years

Over 3 years

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

Yes No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

Yes No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

Yes No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

Yes No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

Yes No

Please give details, or justify if not registering the research.

The trial will be registered with ISCRTN and EudraCT.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- Peer reviewed scientific journals
- Internal report
- Conference presentation

- Publication on website
- Other publication
- Submission to regulatory authorities
- Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- No plans to report or disseminate the results
- Other (please specify)

A53. Will you inform participants of the results?

Yes No

Please give details of how you will inform participants or justify if not doing so.

Patients who agree to take part in the follow up will receive a lay summary of the results.

5. Scientific and Statistical Review**A54. How has the scientific quality of the research been assessed? Tick as appropriate:**

- Independent external review
- Review within a company
- Review within a multi-centre research group
- Review within the Chief Investigator's institution or host organisation
- Review within the research team
- Review by educational supervisor
- Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- Review by independent statistician commissioned by funder or sponsor
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator's institution
- Review by a statistician within the research team or multi-centre group
- Review by educational supervisor
- Other review by individual with relevant statistical expertise
- No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title Forename/Initials Surname

	Title Forename/Initials Surname
	██████████ ██████████
Department	Warwick Clinical Trials Unit
Institution	University of Warwick
Work Address	Gibbet Hill Road Coventry
Post Code	CV4 7AL
Telephone	
Fax	
Mobile	
E-mail	████████████████████

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Survival to 30 days post cardiac arrest.

A58. What are the secondary outcome measures? (if any)

1. Survived event (sustained ROSC, with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital)
2. Survival to hospital discharge (the point at which the patient is discharged from the hospital acute care unit regardless of neurological status, outcome or destination) 3, 6 and 12 months
3. Neurological outcome (modified Rankin Scale (mRS)) at hospital discharge, 3 and 6 months
4. Neurological outcomes (IQCODE and "Two simple questions") at 3 and 6 months
5. Health related quality of life at 3 and 6 months (SF12 and EQ-5D)
6. Cognitive outcome at 3 months (Mini Mental State Examination (MMSE))
7. Anxiety and depression at 3 months (Hospital Anxiety and Depression Scale (HADS))
8. Post Traumatic Stress at 3 months (PTSD civilian checklist (PCL-C))
9. Hospital length of stay
10. Intensive care length of stay

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.

Total UK sample size:	8000
Total international sample size (including UK):	0
Total in European Economic Area:	0

Further details:

4000 patients will receive adrenaline, 4000 patients will receive placebo.

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

The target sample size will be 8,000, which is expected to give a width of the 95% CI for the risk ratio of approximately 0.4 or slightly less; for a risk ratio of 1.25 the 95% CI is 1.07 to 1.46, and for risk ratio of 1.0 it is 0.84 to 1.19. There is a trade-off between precision and practicality in setting a target sample size; above 8,000, there is only a small improvement in precision, but the difficulty and time needed to recruit this number increase significantly. We expect a very small amount of missing data for survival outcomes; in PARAMEDIC we have ascertained survival status for over 99% of randomised patients, and we have therefore not adjusted the sample size estimates to account for missing data.

Using a conventional sample size calculation based on a significance test, a sample size of 8,000 would have 93% power to achieve a statistically significant ($p < 0.05$) result if the true treatment difference is a risk ratio of 1.33 (increase from 6% in adrenaline group to 8% in placebo group), or 75% power if the true treatment difference is a risk ratio of 1.25 (increase from 6% to 7.5%).

A61. Will participants be allocated to groups at random?

Date: 07/03/2014
 Yes No

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147538/575440/1/735

If yes, please give details of the intended method of randomisation:

A61. Will participants be allocated to groups at random?

Yes No

If yes, please give details of the intended method of randomisation:
 Recruitment takes place in an emergency situation therefore telephone or internet randomisation is impractical, the trial will therefore use a system of pre-randomised treatment packs. Trial drugs will be packaged in numbered treatment packs. The pre-randomised sequence will be prepared by the trial statistician. All packs will be identical in appearance; hence clinicians, patients and trial personnel will be unaware of whether any specific pack contains adrenaline or placebo. Treatment packs will be supplied to each ambulance service, in a central location and will be distributed from there to participating ambulance stations and vehicles. When ambulance service personnel identify an eligible patient, randomisation will be achieved by opening one of the packs carried by the vehicle attending the arrest.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The primary analyses will be by intention to treat.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

Title	Forename/Initials	Surname
Prof	[REDACTED]	[REDACTED]
Post	Professor of Emergency Medicine	
Qualifications	[REDACTED]	
Employer	University of Warwick	
Work Address	Medical School Gibbet Hill ROad	
Post Code	CV4 7AL	
Telephone		
Fax		
Mobile		
Work Email	[REDACTED]	
Title	Forename/Initials	Surname
	[REDACTED]	[REDACTED]
Post	Patient Representative	
Qualifications	[REDACTED]	
Employer	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
Telephone		
Fax		
Mobile		
Work Email	[REDACTED]	
Title	Forename/Initials	Surname
	[REDACTED]	[REDACTED]
Post	Co-Director	
Qualifications	[REDACTED], Certificate	

Date: 07/03/2014 19 147538/575440/1/735

Title Forename/Initials Surname
 Prof [REDACTED] [REDACTED]
 Post Co-Director
 Qualifications [REDACTED]
 Employer Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU)
 Work Address School of Nursing & Midwifery
 Curtin University
 GPO Box U1987 Perth, WA
 Post Code 6845
 Telephone
 Fax
 Mobile
 Work Email [REDACTED]

Title Forename/Initials Surname
 [REDACTED] [REDACTED]
 Post Research & Development Lead
 Qualifications [REDACTED]
 Employer Welsh Ambulance Service
 Work Address Prehospital Emergency Research Unit
 Finance Building, Lansdowne Site,
 Sanatorium Road, Cardiff
 Post Code CF11 8PL
 Telephone
 Fax
 Mobile
 Work Email [REDACTED]

Title Forename/Initials Surname
 Dr [REDACTED] [REDACTED]
 Post Consultant Anaesthetist
 Qualifications [REDACTED]
 Employer Royal United Hospital Bath NHS Trust
 Work Address Department of Anaesthesia and Intensive Care Medicine
 Combe Park
 Bath
 Post Code BA1 3NG
 Telephone
 Fax
 Mobile
 Work Email [REDACTED]

Title Forename/Initials Surname
 Dr [REDACTED] [REDACTED]
 Post Head of Clinical Audit & Research
 Qualifications
 Employer London Ambulance Service NHS Trust
 Work Address Clinical Audit & Research Unit
 London Ambulance Service NHS Trust
 8-20 Pocock Street, London

NHS REC Form
Work Address

Clinical Audit & Research Unit
London Ambulance Service NHS Trust
8-20 Pocock Street, London

Post Code SE1 8SD

Telephone

Fax

Mobile

Work Email

Title Forename/Initials Surname

Prof [REDACTED] [REDACTED]

Post Professor of Clinical Practice

Qualifications [REDACTED]

Employer Univeristy of Surrey

Work Address Duke of Kent Building

University of Surrey

Guildford

Post Code GU2 7TE

Telephone

Fax

Mobile

Work Email

Title Forename/Initials Surname

Prof [REDACTED] [REDACTED]

Post Professor of Health Economics

Qualifications [REDACTED]

Employer University of Warwick

Work Address Warwick Clinical Trials Unit

Gibbet Hill Road

Coventry

Post Code CV4 7AL

Telephone

Fax

Mobile

Work Email

Title Forename/Initials Surname

Prof [REDACTED] [REDACTED]

Post

Qualifications [REDACTED]

Employer University of Warwick

Work Address Gibbet Hill Road

Coventry

Post Code CV4 7AL

Telephone

Fax

Mobile

Work Email

Title Forename/Initials Surname

[REDACTED] [REDACTED]

Date: 07/03/2014

Post Co-Director of Oxford Clinical Trials Research Unit

Qualifications [REDACTED]

Employer University of Oxford

Title Forename/Initials Surname
Prof [REDACTED] [REDACTED]
Post Co-Director of Oxford Clinical Trials Research Unit
Qualifications [REDACTED]
Employer University of Oxford
Work Address

Post Code
Telephone
Fax
Mobile
Work Email [REDACTED]

Title Forename/Initials Surname
[REDACTED] [REDACTED]
Post Associate Professor
Qualifications [REDACTED]
Employer University of Warwick
Work Address Warwick Medical School

Gibbet Hill Road
Coventry
Post Code CV4 7AL
Telephone
Fax
Mobile
Work Email [REDACTED]

Title Forename/Initials Surname
[REDACTED] [REDACTED]
Post Medical Director
Qualifications [REDACTED]
Employer North East Ambulance Service NHS Trust
Work Address Bernicia House, Goldcrest Way

Newburn Riverside
Newcastle Upon Tyne
Post Code NE15 8NY
Telephone
Fax
Mobile
Work Email [REDACTED]

Title Forename/Initials Surname
[REDACTED] [REDACTED]
Post Divisional Medical Director
Qualifications [REDACTED]
Employer South Central Ambulance Service NHS Trust
Work Address

Post Code
Telephone
Fax
Mobile
Work Email [REDACTED]

Post Code
Telephone
Fax
Mobile
Work Email

[Redacted]

Title Forename/Initials Surname

[Redacted] [Redacted]

Post
Qualifications
Employer
Work Address

Principal Research Fellow

PhD

University of Warwick

Warwick Clinical Trials Unit

Gibbet Hill Road

Coventry

Post Code
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Fax
Mobile
Work Email

CV4 7AL

[Redacted]

Title Forename/Initials Surname

[Redacted] [Redacted]

Post
Qualifications
Employer
Work Address

Co-Director

[Redacted]

Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU)

School of Nursing & Midwifery

Curtin Unviersity

GPO Box U1987 Perth,

Post Code
Telephone
Fax
Mobile
Work Email

6845

[Redacted]

Title Forename/Initials Surname

[Redacted] [Redacted]

Post
Qualifications
Employer
Work Address

Medical Director

[Redacted]

West Midlands Ambulance Service NHS Trust

Millenium Point

Waterfront Business Park

Waterfront Way, Brierley Hill

Post Code
Telephone
Fax
Mobile
Work Email

DY5 1LX

[Redacted]

Title Forename/Initials Surname

[Redacted] [Redacted]

Post
Qualifications
Employer
Work Address

Professor of Clinical Trials

University of Warwick

Warwick Clinical Trials Unit

Title Forename/Initials Surname
 [Redacted] [Redacted]
 Post Professor of Clinical Trials
 Qualifications
 Employer University of Warwick
 Work Address Warwick Clinical Trials Unit
 Gibbet Hill Road
 Coventry
 Post Code CV4 7AL
 Telephone
 Fax
 Mobile
 Work Email [Redacted]

A64. Details of research sponsor(s)

A64-1. Sponsor

SP1

Status: NHS or HSC care organisation Commercial status: Non-Commercial
 Academic
 Pharmaceutical industry
 Medical device industry
 Other

If Other, please specify:

Contact person

Name of organisation University of Warwick
 Given name [Redacted]
 Family name [Redacted]
 Address Medical School, Gibbet Hill Road
 Town/city Coventry
 Post code CV4 7AL
 Country UNITED KINGDOM
 Telephone
 Fax
 E-mail wmssponsorship@warwick.ac.uk

Legal representative in the European Economic Area for the purpose of this trial

A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal Representative

Contact person

Name of organisation
 Given name
 Family name
 Address
 Town/city
 Post code

Given name
 Family name
 Address
 Town/city
 Post code
 Country
 Telephone
 Fax
 E-mail

A65. Has external funding for the research been secured?

- Funding secured from one or more funders
 External funding application to one or more funders in progress
 No application for external funding will be made

What type of research project is this?

- Standalone project
 Project that is part of a programme grant
 Project that is part of a Centre grant
 Project that is part of a fellowship/ personal award/ research training award
 Other

Other – please state:

Please give details of funding applications.

Organisation The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
 Address University of Southampton
 Alpha House
 Enterprise Road, Southampton
 Post Code SO16 7NS
 Telephone 02380595586
 Fax
 Mobile
 Email info@netscc.ac.uk

Funding Application Status: Secured In progress

Amount: £2,724,486

Duration

Years: 4

Months: 6

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

Yes No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title Forename/Initials Surname
	██████████ ██████████
Organisation	West Midlands (South) Comprehensive Local Research Network
Address	University Hospitals Coventry & Warwickshire NHS Trust
	Fourth Floor Rotunda (ADA40007)
	University Hospital, Clifford Bridge Road
Post Code	CV2 2DX
Work Email	██
Telephone	██████████
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A68-2. Select Comprehensive Local Research Network for this NHS organisation:

To support communication between the REC and R&D contacts for this study, please select the Comprehensive Local Research Network (CLRN) for this NHS organisation. This CLRN will be the Lead CLRN for your study.

West Midlands (South)

For information about support and advice available through the Lead CLRN and the CLRNs for participating sites see http://www.crncc.nihr.ac.uk/about_us/processes/csp. A map showing the CLRNs is available at http://www.crncc.nihr.ac.uk/about_us/ccrn.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/03/2014
 Planned end date: 31/08/2018
 Total duration:
 Years: 4 Months: 6 Days:

A69-2. How long do you expect the study to last in all countries?

Planned start date: 01/03/2014
 Planned end date: 31/08/2018
 Total duration:
 Years: 4 Months: 6 Days:

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial ⁽¹⁾

The trial will end when the last data is entered into the database which could be the last follow up visit or HES data received.

A71-2. Where will the research take place? (Tick as appropriate)

- England
 Scotland
 Wales
 Northern Ireland
 Other countries in European Economic Area

Total UK sites in study 87

Does this trial involve countries outside the EU?

Yes No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:

- | | |
|--|----|
| <input checked="" type="checkbox"/> NHS organisations in England | 73 |
| <input checked="" type="checkbox"/> NHS organisations in Wales | 14 |
| <input type="checkbox"/> NHS organisations in Scotland | |
| <input type="checkbox"/> HSC organisations in Northern Ireland | |
| <input type="checkbox"/> GP practices in England | |
| <input type="checkbox"/> GP practices in Wales | |
| <input type="checkbox"/> GP practices in Scotland | |
| <input type="checkbox"/> GP practices in Northern Ireland | |
| <input type="checkbox"/> Social care organisations | |
| <input type="checkbox"/> Phase 1 trial units | |
| <input type="checkbox"/> Prison establishments | |
| <input type="checkbox"/> Probation areas | |
| <input type="checkbox"/> Independent hospitals | |
| <input type="checkbox"/> Educational establishments | |
| <input type="checkbox"/> Independent research units | |
| <input type="checkbox"/> Other (give details) | |

Acute Trusts will have a single SSI

Total UK sites in study: 87

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will monitor the accumulating outcome data, and one of their roles is to recommend cessation of recruitment if a clear result has been reached (i.e. if either adrenaline or placebo is clearly superior). Recruitment will continue during this period. Initial monitoring will be every 3 months.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive

summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

We suggest that different thresholds of evidence for early termination are adopted for standard care (adrenaline) or placebo being more effective, as it is likely that stronger evidence would be needed to change current standard practice (adrenaline use) if placebo is found to be superior or if adrenaline is superior the trial will stop quickly and ambulance services will revert to standard care. We therefore propose that interim analyses are conducted frequently in the early stages of the trial, so that, if adrenaline is superior, this can be detected early. Thus we will minimise any risks to patients while producing robust evidence that will change practice.

The outcomes of primary interest for interim analyses are 30 day survival and neurological status. We propose to prepare reports for the DMC initially on a three monthly basis. The exact schedule of interim analyses and the nature of any early stopping rules will be determined by the DMC, in discussion with the investigators, before the start of recruitment.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- NHS indemnity scheme will apply (NHS sponsors only)
- Other insurance or indemnity arrangements will apply (give details below)

The University has in force a Public and Products Liability policy and a Clinical Trials Insurance Policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage subject to the terms, conditions and exceptions of the policy.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- Other insurance or indemnity arrangements will apply (give details below)

The University has in force a Public and Products Liability policy and a Clinical Trials Insurance which provides cover for claims for "negligent harm" and the activities here are included within that coverage subject to the terms, conditions and exceptions of the policy.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at

these sites and provide evidence.

- NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
 Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

NHS indemnity covers NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

Negligent harm cover will be provided by standard NHS arrangements. NHS Indemnity does not give indemnity for compensation in the event of non-negligent harm, so no specific arrangements exist for non-negligent harm for this trial.

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

Yes No

Please enclose a copy of relevant documents.

Part B Section 1: Investigational Medicinal Products**Information on each IMP.**

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable.

If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance. Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question 13 using the navigation screen.

Investigational medicinal products

PR1 Adrenaline

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR1**

Investigational medicinal product category:

14. STATUS OF THE IMP

If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation? Yes No Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

 Yes No Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

 Yes No Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group

 Yes No Not Answered

Other :

 Yes No Not Answered**14-3. IMPD submitted:**

Full IMPD

 Yes No Not Answered

Simplified IMPD

Yes No Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

Yes No Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

Yes No Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

Yes No Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

Yes No Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

Yes No Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

Yes No Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Adrenaline
Product code where applicable	
ATC codes, if officially registered	
Pharmaceutical form (use standard terms)	Solution for injection in pre-filled syringe
Is this a specific paediatric formulation?	<input type="radio"/> Yes <input checked="" type="radio"/> No <input type="radio"/> Not Answered
Maximum duration of treatment of a subject according to the protocol	

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total: per day total Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed

Specify per day or total per day total Not Answered

Specify total dose (number and unit) mg
milligram
(s)

Route of administration (relevant to the maximum dose): Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Ephinephrine Hydrogentartrate

CAS number: 51-42-3

Current sponsor code:

Other descriptive name: Adrenaline Tartrate

Full Molecular formula C13H19NO9

Chemical/biological description of the Active Substance

Strength

Concentration unit: mg milligram(s)

Concentration type: equal

Concentration number (only use both fields for range): 1.82

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? Yes No Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP)) Yes No Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾ Yes No Not Answered

- Combination product that includes a device, but does not involve an Advanced Therapy Yes No Not Answered
- Radiopharmaceutical medicinal product? Yes No Not Answered
- Immunological medicinal product (e.g. vaccine, allergen, immune serum)? Yes No Not Answered
- Plasma derived medicinal product? Yes No Not Answered
- Extractive medicinal product? Yes No Not Answered
- Recombinant medicinal product? Yes No Not Answered
- Medicinal product containing genetically modified organisms? Yes No Not Answered
- Herbal medicinal product? Yes No Not Answered
- Homeopathic medicinal product? Yes No Not Answered
- Another type of medicinal product? Yes No Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Adrenaline is a direct acting sympathomimetic agent.

Is it an IMP to be used in a first-in-human clinical trial? Yes No Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

Information on Placebo

13. Is a there a placebo: Yes No**PL1**

Pharmaceutical form:

Solution for injection in pre-filled syringe

Route of administration:

Intravenous Use

Which IMP is it a placebo for? Specify IMP Number(s) from IMPs list

IMP 1

PR1

Composition, apart from the active substance(s):

Is it otherwise identical to the IMP?

 Yes No

Part B: Section 6 - Adults unable to consent for themselves**A. Clinical trials of investigational medicinal products**

In this sub-section, an adult means a person aged 16 or over.

A1. What clinical condition(s) will the participants have? *The trial must relate directly to this condition.*

Out of Hospital Cardiac Arrest

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

Yes No

A3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

The Research Paramedics will be fully trained on informed consent and assessing capacity, GCP guidelines, relevant legislation and the trial related procedures around consent.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? *You may refer back to your answer to Question A24.*

There is the potential amongst patients who receive adrenaline that a greater number will have their hearts re-started and will survive in the short term (mins to hours).

The available evidence on long-term survival (survival to hospital discharge) suggests that some participants who are randomised to placebo will survive to leave hospital when they would have died if they had received adrenaline; that is they will survive as a result of participating in the trial. Participants receiving placebo may also avoid the potential side effects of adrenaline (irregular heart beat, adverse effects on metabolics, brain injury).

Participation in the study will provide critical information about the most effective way to resuscitate future patients that sustain an out of hospital cardiac arrest.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

Yes No

If Yes, please give an assessment below. You may refer back to your answers to Questions A22 and A23. Highlight any risk, burden or discomfort specific to these participants. Justify in relation to the potential benefits.

Risks and burdens: A fundamental issue in this trial is the question of whether the current evidence on the use of adrenaline in cardiac arrest raises sufficient doubt about its efficacy and concern about its potential harm to justify a trial that involves withholding adrenaline from some participants. Most clinical drug trials involve either the comparison of a new drug with the current best treatment or in cases where no current best treatment exists, with a placebo. This trial is unusual in that the underlying hypothesis is that current best practice may be harmful therefore it is ethically necessary to seek evidence to confirm or refute this hypothesis, and that this evidence can only reliably be obtained by a trial that includes participants who do not receive currently recommended treatment. The aim is not to investigate whether another drug is better than adrenaline but to investigate whether adrenaline is more harmful than no adrenaline. The hypothesis that adrenaline is harmful raises the question of what is meant by harm. As we have outlined in our review of current evidence, there is evidence that adrenaline as currently used improves the rate of return of spontaneous circulation (ROSC). Thus it is possible that some people who are entered into the trial and are randomised to receive placebo may fail to achieve return of spontaneous circulation as a result of participating in the trial. However the available evidence on long-term survival (survival to hospital discharge) suggests that some participants who are randomised to placebo will survive to leave hospital when they would have died if they had received adrenaline; that is they will survive as a result of participating in the trial. So for individual participants there is a risk/benefit trade-off for participation which is uncertain because we cannot know on an individual patient basis which person will benefit from the adrenaline and who will be harmed by it.

The current evidence suggests that more people will be harmed than will benefit (if we consider survival to discharge more beneficial than initial survival followed by early death). However the evidence is not so strong that we can say adrenaline should not be used. As we have shown in our survey of practitioners there is equipoise on this question. Given the uncertainty of the evidence, and the life threatening nature of the condition being treated, it is ethically important that we obtain the best evidence we can to justify treatment, while ensuring that the interests of the research participants remain paramount. In considering the interests of the research participants the question is whether for any individual participant the benefits of participating outweigh the risk of harm, or at least the harm/benefit balance is neutral. Based on current evidence it would seem that risks and benefits from participating in this trial are reasonably balanced (if a participant is randomised to placebo they may have a reduced chance of immediate survival but an increased chance of surviving to leave hospital. Our initial PPI work suggest that members of the public weigh long term survival higher than short term recovery of spontaneous circulation so it would seem reasonable to assume potential participants might agree to taking part if they were able to do so.

Minimising risk

The study will be overseen by a Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) appointed by the National Institute for Health Research Health Technology Assessment Programme Director. The majority of members of the TSC will be independent from the study investigators. All members of the DMC will be independent. The study Chief Investigators and other members of the study team may attend meetings in an advisory capacity at the request of the DMC chair.

The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The Data Monitoring Committee (DMC) will monitor safety in this trial. The outcomes of primary interest are long-term outcomes (30 day survival and neurological status). We will regularly prepare reports for the DMC initially at an interval to be confirmed by that group. The DMC will determine the nature of any early stopping rules. We suggest a differing threshold is adopted for early termination if standard care (adrenaline) is more effective compared to if placebo is more effective. This is based on a combination of minimising any risks to patients whilst producing robust evidence that will change practice. We suggest that the balance of evidence that would be needed to change current standard practice (adrenaline use) to be greater.

Patient and public involvement. Because of the particular ethical difficulty of conducting a trial which involves withholding a standard treatment, and the major life changing impact on participants, it will be imperative to have procedures for close surveillance of trial data. To address these concerns we will include two PPI representatives in the Trial Steering Committee.

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

In this setting it will not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying emergency treatment.

We consider it unlikely that even if it were possible to seek consent from a personal legal representative, that in light of the emotional distress of the cardiac arrest will cause, that any such person would be likely to have the capacity to make an informed decision in the limited time available.

A7. Is it possible that a participant requiring urgent treatment might need to be recruited into the trial before it is possible to identify and seek consent from a legal representative?

Yes No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or a legal representative as soon as practicable thereafter.

The clinical trial relates directly to the treatment of cardiac arrest, which is a life-threatening emergency. All patients that suffer a cardiac arrest will lack capacity. There are no alternative groups of patients amongst whom this research could be conducted.

All patients will lack capacity throughout the intervention period of the trial due to the nature of the underlying medical condition (cardiac arrest).

The occurrence of an out of hospital cardiac arrest is unpredictable. Within seconds of cardiac arrest a person

becomes unconscious and thus incapacitated. It will not therefore be possible to obtain prospective consent directly from the research participant.

Treatment (in the form of CPR) must be started immediately in an attempt to save the person's life. Delay in the initiation of CPR and other emergency treatment (e.g. defibrillation) is associated with worse outcomes. Observational studies suggest that if adrenaline is effective, the earlier it is given the more likely it will be beneficial.

In this setting it will not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying emergency treatment.

We consider it unlikely that even if it were possible to seek consent from a personal legal representative, that in light of the emotional distress of the cardiac arrest will cause, that any such person would be likely to have the capacity to make an informed decision in the limited time available.

A8. What arrangements will be made to continue to consult legal representatives during the course of the research where necessary?

For surviving patients, in the event that a patient lacks capacity to consent to continue to take part in the study, the Research Paramedic will work with the hospital team to identify a legal representative.

The legal representative will be approached and be provided with the information sheet explaining the trial and the options for theirs and the patient's involvement, including the need for them to give consent on behalf of the patient and complete questionnaires on behalf of the patient. The legal representative will then have time to consider the information provided. The Research Paramedic or hospital team will then ask when the legal representative would like someone to come back to discuss participation further and potentially take consent.

The legal representative may decide it is not an appropriate time to discuss the trial or they may decide that the patient would not want to take part in which case their feelings will be respected and their decision about taking part will be recorded.

It is possible that the patient will have regained capacity by the time the 3 month visit is due. When contacting the legal representative to arrange the 3 month visit, we will ask if we can speak with the patient. If on assessment of the patient either on the phone or on the visit it is found that the patient still lacks capacity the legal representative will be asked to complete the questionnaires on behalf of the patient. If the patient has capacity then information will be provided about the trial and consent sought.

A9. Will steps be taken to provide information about the trial to participants, according to their capacity of understanding, and to consider the wishes of participants capable of forming an opinion?

Yes No

If Yes, give details.

The first attempt to contact the patient and inform them of their enrolment into the trial will be during their stay in hospital before hospital discharge. We plan to make contact as soon as practically possible after the initial emergency has passed and taking the utmost care and sensitivity in doing so. Following our experience from a 4,400 patient study in out of hospital cardiac arrest (PARAMEDIC trial) and talking to fellow researchers from the REVIVE cardiac arrest study and discussions with patient and public representatives, we believe the earliest practicable time to contact patients and relatives is once the patient is discharged from ICU and is on a hospital ward by which time initial emergency will have passed. This allows sufficient time for the research team to be made aware of enrolment, identify who the patient is, check which hospital the patient was transferred to, whether they are still alive and to verify with the hospital team where the patient is within the hospital. Transfer to a ward will indicate that the initial emergency has passed and the patient's condition will have stabilised. It is also more likely that the patient has regained consciousness and it will avoid any confusion or additional distress of making an approach while the patient remains critically ill in intensive care.

Procedure

The Research Paramedic, or hospital team will assess if the patient has capacity to consent. If the patient has capacity, they will be provided with the information sheet explaining the trial and the options for their involvement. The patient will be allowed time to consider the information provided, have the opportunity to ask questions and discuss with others. The Research Paramedic or hospital team will then ask when the patient would like someone to come back to discuss participation further and potentially take consent.

The patient may decide it is not an appropriate time to discuss the trial or they may decide that they do not want to be involved in which case their feelings will be respected and their decision about continuing in the trial will be recorded.

We anticipate this will be a very small group of patients per month per hospital.

A10-1. What will be the criteria for withdrawal of participants?

A patient or their legal representative can withdraw from the trial at any point. If a patient declines to take part in the follow up visits we will check that they are happy for us to continue to collect data on their stay in hospital and recovery to 12 months.

A10-2. Where a participant is recruited prior to consent being obtained, and consent is later withheld or the participant dies before consent can be given, what provisions will apply to the study data collected up to this point?

In the event that a patient dies prior to obtaining consent from them or their legal representative, we will continue to use the study data collected up until that point.

At the point of seeking consent from the patient or their legal representative the study intervention will have ceased and the patient will be during a period of follow-up. We will therefore seek consent to continue in the follow-up phase of the trial. In the event that a participant declines follow-up we will establish whether they agree to us to continue to collect information about their health from information sources such as their medical records and the Health and Social Care Information Centre. In the event that the patient declines both the face to face and remote follow-up they will be withdrawn from further data collection.

Based on our experience in previous trials it is exceptionally rare that a patient or legal representative will request withdrawal of study data already collected. Post randomisation exclusions run the risk of introducing significant bias which would be likely to damage the validity of the findings of this research. In the event of such a request we would remove all identifiable information relating to that subject but it is our intention to include the baseline and primary outcome data for all patients in the study. Any requests to withdraw all data already collected will be assessed by the Data Monitoring Committee who will provide an opinion about the consequences of the withdrawal of that data to the Research Ethics Committee on a case by case basis.

Part B: Section 8 - Additional information for applications to National Information Governance Board for Health and Social Care Responses to frequently asked questions on NIGB applications are available at <http://www.nigb.nhs.uk/ecc/eccfrequently>

1. Do you plan to extract data from Hospital Episode Statistics (HES) or the Secondary Uses Service (SUS)?

Yes No

16. Do you have anything to add in support of the application, which is not included elsewhere on the form?

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

Investigator identifier	Research site	Investigator Name
IN1 <input type="checkbox"/>	<input checked="" type="radio"/> NHS site <input type="radio"/> Non-NHS site Country: England Organisation name: WEST MIDLANDS AMBULANCE SERVICE NHS TRUST Address: WATERFRONT BUSINESS PARK, WATERFRONT WAY, BRIERLEY HILL WEST, MIDLANDS Post Code: DY5 1LX	Forename: [REDACTED] Middle name: [REDACTED] Family name: [REDACTED] Email: [REDACTED] Qualification (MD...): [REDACTED] Country: UNITED KINGDOM
IN2 <input type="checkbox"/>	<input checked="" type="radio"/> NHS site <input type="radio"/> Non-NHS site Country: England Organisation name: NORTH EAST AMBULANCE SERVICE NHS TRUST Address: BENICIA HOUSE, GOLDCREST WAY, NEWBURN RIVERSIDE, NEWCASTLE UPON TYNE TYNE AND WEAR Post Code: NE15 8NY	Forename: [REDACTED] Middle name: [REDACTED] Family name: [REDACTED] Email: [REDACTED] Qualification (MD...): [REDACTED] Country: UNITED KINGDOM
IN3 <input type="checkbox"/>	<input checked="" type="radio"/> NHS site <input type="radio"/> Non-NHS site Country: England Organisation name: SOUTH CENTRAL AMBULANCE SERV NHS TRUST Address: SOUTHERN HOUSE	Forename: [REDACTED] Middle name: [REDACTED] Family name: [REDACTED] Email: [REDACTED] Qualification (MD...): [REDACTED] Country: UNITED KINGDOM

Country: England

Family name [REDACTED]

Email [REDACTED]

Qualification (MD...) [REDACTED]

Country UNITED KINGDOM

Organisation name SOUTH CENTRAL AMBULANCE SERV NHS TRUST

Address SOUTHERN HOUSE SPARROWGROVE, OTTERBOURNE WINCHESTER

Post Code SO21 2RU

IN4

NHS site

Non-NHS site

Country: Wales

Forename [REDACTED]

Middle name [REDACTED]

Family name [REDACTED]

Email [REDACTED]

Qualification (MD...) [REDACTED]

Country UNITED KINGDOM

Institution name Welsh Ambulance Service

Department name

Street address Prehospital Emergency Research Unit

Town/city Finance Building, Lansdowne Site,

Post Code CF11 8PL

IN5

NHS site

Non-NHS site

Country: England

Forename [REDACTED]

Middle name [REDACTED]

Family name [REDACTED]

Email [REDACTED]@lond-amb.nhs.uk

Qualification (MD...)

Country UNITED KINGDOM

Organisation name LONDON AMBULANCE SERVICE NHS TRUST

Address 220 WATERLOO ROAD

Post Code LONDON GREATER LONDON SE1 8SD

IN24

NHS site

Non-NHS site

Country: England

Forename [REDACTED]

Middle name [REDACTED]

Family name [REDACTED]

Email [REDACTED]

Qualification (MD...)

Country [REDACTED]

Organisation name UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST

Address WALSGRAVE GENERAL HOSPITAL 41 CLIFFORD BRIDGE ROAD COVENTRY WEST MIDLANDS

Organisation name	UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST	Country
Address	WALSGRAVE GENERAL HOSPITAL CLIFFORD BRIDGE ROAD COVENTRY WEST MIDLANDS	
Post Code	CV2 2DX	

PART D: Declarations**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
 - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
 - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
 - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
 - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
 - May be sent by email to REC members.
10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.
12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further

Contact point for publication (Not applicable for R&D Forms)

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator
- Sponsor
- Study co-ordinator
- Student
- Other – please give details
- None

Access to application for training purposes (Not applicable for R&D Forms)

Optional – please tick as appropriate:

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Prof Gavin Perkins on 06/03/2014 09:03.

Job Title/Post: Professor
 Organisation: University of Warwick
 Email: [REDACTED]
 Signature:
 Print Name:
 Date: (dd/mm/yyyy)

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

Date: 07/03/2014

8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.
8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

This section was signed electronically by Mrs Jane Prewett on 06/03/2014 09:52.

Job Title/Post: Deputy Director, RSS

Organisation: University of Warwick

Email: [REDACTED]