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 complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
PARAMEDIC-3

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

( ) Yes (●) No

2b. 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)*

- [x] England
- [ ] Scotland
- [x] 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 applications do you require?

- [x] IRAS Form
- [x] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

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

( ) Yes (•) No

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

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR Medtech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

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 Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN.

Submission of a Portfolio Application Form (PAF) is no longer required.

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 Confidentiality Advisory Group 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 Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

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 familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
PARAMEDIC-3

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

REC Name:
South Central - Oxford C Research Ethics Committee

REC Reference Number:
21/SC/0178

Submission date:
11/05/2021

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Pre-hospitAl RAndomised trial of MEDICation route in out-of-hospital cardiac arrest (PARAMEDIC3)

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Prof	Gavin	Perkins
Post	Professor in Critical Care Medicine		
Qualifications	MB ChB, MD, FFIMC, FICM, FERC, FRCP, FMedSci		
ORCID ID	0000 0003 3027 7548		
Employer	University of Warwick		
Work Address	Gibbet Hill Road		
	Coventry		
Post Code	CV4 7AL		
Work E-mail	g.d.perkins@warwick.ac.uk		
* Personal E-mail			
Work Telephone	02476 150925		
* Personal Telephone/Mobile			

Fax

** 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 HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Mrs	Carole	Harris
Address	University of Warwick, Research & Impact Services, University House		
	Kirby Corner Road		
	Coventry		
Post Code	CV4 8UW		
E-mail	sponsorship@warwick.ac.uk		
Telephone	024 765 75733		
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):	SOC.20/20-21
Sponsor's/protocol number:	SOC.20/20-21
Protocol Version:	1.0
Protocol Date:	11/05/2021
Funder's reference number (enter the reference number or state not applicable):	NIHR131105
Project website:	https://warwick.ac.uk/fac/sci/med/research/ctu/trials/paramedic3

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. 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):

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.

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 Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Each year over 30,000 people's hearts suddenly stop beating in communities around the UK (a condition known as out-of-hospital cardiac arrest). Giving drugs, such as adrenaline, is very effective at restarting the heart. However, for many people drugs are given too late to save them. This partly explains why less than one in ten people survive an out of hospital cardiac arrest.

Current guidelines advise paramedics to inject drugs into a vein. It can take several critical minutes to put a drip in to a vein, ready to give drugs. A faster way to give drugs is to put a small needle into an arm or leg bone. This allows drugs to be given directly into the rich blood supply found in the bone marrow. Currently, none of the existing research is good enough to help paramedics decide how best to treat people with cardiac arrest.

The aim of the trial is to find out if giving drugs through a vein or into the bone is the most effective way to treat someone when their heart suddenly stops working and whether it makes a difference to how well people recover after cardiac arrest.

We plan to test whether injecting drugs into the vein or the bone is most effective. NHS paramedics in England and Wales will recruit 15,000 patients to the trial- half will receive drugs given into the bone and half will receive drugs given into the vein. This will be decided by chance. This is known as a randomised controlled trial, and is the best way of finding out which treatment is most effective

We will follow-up patients that survive their cardiac arrest to see how they well they recover from their 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, HRA, 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.

We have identified the key issues as: consent, confidentiality, safety, and information provision to families of non-survivors.

1) CONSENT
This trial will recruit cardiac arrest patients in an out-of-hospital setting. Out-of-hospital cardiac arrest is a sudden and unpredictable event that immediately renders the patient unconscious, such that they lack mental capacity. Treatment must be started immediately to maximise the likelihood of patient survival. In this context, it would not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying treatment.

We have identified the only practical way to proceed as reliance on a deferred consent model, approved by a Research Ethics Committee. We have carefully considered the framework for deferred consent in emergency research, developed by the Health Research Authority in accordance with the Mental Capacity Act 2005. Following the emergency, we will inform the participant or their consultee (if the participant lacks mental capacity) of trial enrolment and seek consent for completion patient-reported outcome measures.

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation (e.g. Mental Capacity Act 2005), the emergency framework for deferred consent and University of Warwick Clinical Trials Unit Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 2018.

The approach is supported by our trial PPI panel.

2) CONFIDENTIALITY
We are seeking approval from the Confidentiality Advisory Group (CAG) to access and process patient identifiable information without consent. The NHS Act 2006 and the regulations enable the common law duty of confidentiality to

be temporarily lifted so that confidential patient information can be transferred to the applicant without the discloser (NHS site and national databases (e.g. NHS Digital)) being in breach of the common law duty of confidentiality. We present the potential risks, mitigations and benefits of this approach below.

The main risk for access patient identifiable information from clinical records relates to a breach of trust/confidentiality through access to clinical records.

We are mitigating the risk by:
(1) Collecting the minimum amount of data to address this research question
(2) Retrospectively retrieving patient consent or consultee agreement in those that survive for ongoing data collection with the option of withdrawal if they do not wish to participate
(3) Ensuring staff collecting the data will have a duty of confidentiality through relevant contracts.

The direct benefits to current and future patients is that we will be able to determine how best to treat patients that experience an out-of-hospital cardiac arrest patients by ensuring that trial data is of high-quality and reliable.

Considering the risks, mitigations and benefits we assess the overall risks from this to be justified. The research requires the research team to access the following identifiable information from the patient's clinical records:
1) NHS Number
2) Date of birth
3) Postcode
4) Initials
5) Ethnicity
6) Date of death (where applicable)

The information will be linked by NHS number (or other identifiers where NHS number is not available) to:
1) NHS Digital
2) Hospital Episode Statistics
3) The Intensive Care National Audit and Research Centre (ICNARC) case-mix programme
4) Patient Episode Database for Wales PEDW)
5) National Institute for Cardiovascular Outcomes Research (NICOR)
6) ONS Mortality data
7) GP records
8) UK Transplant Registry (UKTR)
9) Out -of-hospital cardiac arrest registry
10) Health Data Research UK (HDR UK)

Our approach seeks to balance respect for the patients right to information in their medical record being treated confidentially, public health interest and need in obtaining an unbiased sample to achieve a valid research outcome, and consideration of practicable alternatives to obtaining consent.

This approach aligns with the approach that we have used in our previous trials. The approach is supported by our trial PPI panel.

3) SAFETY
It is essential that treatment (as per the study arms) is initiated as soon as possible. Delays in treatment initiation may place the patient at risk and increase the likelihood of death. Delays may therefore make study interventions appear less effective by reducing any observed treatment effect. Therefore, the emergency consent research model outlined in the Mental Capacity Act will minimise risk and ensure the safety of those involved. Both interventions are routinely available and used in current NHS clinical practice.

4) INFORMATION PROVISION TO FAMILIES OF NON-SURVIVORS
Survival rates in out-of-hospital cardiac arrest are low, with only around 8% patients surviving to hospital discharge. There is a need to carefully consider how, and if, we inform the loved ones of participants about trial enrolment. At the point of death, there is no legal basis in seeking consent/ agreement for trial participation, such that the purpose of any approach would be to ensure transparency and openness. However, this needs to be balanced against the potential emotional burden placed on relatives if information is provided about the trial following the death of their loved one.

In previous studies (e.g. PARAMEDIC-2), we have adopted an approach of passive information whereby information is placed in the public domain and allows the individual to seek further information, if wanted, at a time that is right for them. Our PPI panel supports using this same approach in this trial. An ongoing small pre-hospital study is exploring the feasibility of actively informing relatives of participants that do not survive about trial participation by letter. We plan to reflect on our current strategy once the results of that study are known.

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)

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

Principal objective

To find out if giving drugs through a vein or into the bone improves survival at 30-days in adults that have an out-of-hospital cardiac arrest.

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

To evaluate the effect of an IO first strategy on neurological outcome, quality of life and survival at other time-points.

To determine the cost-effectiveness of an IO first strategy.

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

Cardiac arrest is an important health condition. NHS ambulance services treat 30,000 patients that have an out-of-hospital cardiac arrest each year. Survival is poor with less than 10% patients surviving to hospital discharge. The main treatments for cardiac arrest are chest compressions (pressing down on the breastbone 100 times per minute), defibrillation (electrical shocks to the heart), artificial ventilations, and drug treatments.

Our previous research (PARAMEDIC-2) has shown that drug treatments are extremely effective at restarting the heart. However, in the the PARAMEDIC-2 trial, drug treatments were given on average 21-minutes after the cardiac arrest. This likely reduces the effectiveness of the treatment. Our statistical analysis showed that, for every one-minute reduction in time to drug treatment survival increased by 0.7%.

Current guidelines advise paramedics to give drugs in to a vein. This route of injection is referred to as the intravenous (IV) route and the problem with this is it can take several critical minutes to put a drip in to a vein, ready to give drugs. It is only if paramedics are unable to insert a drip after two-attempts that they consider using an alternative form of vascular access (intraosseous route- IO).

IO is a newer, faster way of giving drugs in which a small needle into an arm or leg bone. This allows drugs to be injected directly into the rich blood supply found in the bone marrow.

It is currently known whether an strategy in which IO access is attempted first would improve survival. The IO route potentially allows vascular access to be obtained quicker (thereby reducing time to giving life-saving drugs). Some research studies suggest the IO route might be as good, if not better, than injecting drugs in to the vein. Other studies suggest it might not be as good.
Overall, current evidence is not sufficient to support a change in practice.

Data from research audits have found the use of the IO route has double over four years between 2014-2018 and London Ambulance Service reported the amount of money being spent on IO equipment has double over two years. This provides evidence of a change in clinical practice in the absence of evidence.

The International Liaison Committee on Resuscitation (ILCOR) conducted a systematic route in which they evaluated the current studies on IO and IV routes for giving drugs. ILCOR concluded that there was insufficient evidence to support the routine use of IO access. In making this recommendation, ILCOR highlighted urgent need for a randomised controlled trial to determine the most effective approach.

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.*

OBJECTIVES
The primary objective of this trial is to evaluate the effectiveness of using the intraosseous route (small needle into an arm or leg bone) to give drugs to out of hospital cardiac arrest patients measured by survival status at 30 days.

The secondary objectives of the trial are to evaluate the effect of the intraosseous route as paramedics first method of treatment (referred to as first strategy) on the brain function, quality of life and survival of patients at other time points. It will also determine the cost-effectiveness of paramedics using the intraosseous route as their first strategy.

PARTICIPANT IDENTIFICATION AND SCREENING
Participants will be recruited by NHS ambulance clinicians (paramedics, doctors, nurses and other healthcare professionals). On attending an out-of-hospital cardiac arrest, the ambulance clinician will determine the time at which vascular access (ability to insert a small needle in to a patient to give them drugs) is required.

All clinical trials have an inclusion and exclusion criteria referred to as the eligibility criteria which are used to assess whether it is safe and suitable for a patient to enter in to a trial. Once vascular access has been identified the NHS ambulance clinician will decide if the patient is suitable to enter in to the trial using the eligibility criteria set out in the protocol.

To determine eligibility, no additional tests or investigations are required to speed up the process due the urgent need to start treatment. If the patient is deemed eligible, then the patient will proceed to randomisation. The point of randomisation will be the opening of the randomisation envelope (or equivalent).

INTERVENTIONS
Patients will be randomly allocated to receive either IO first strategy (intervention) or IV first strategy (control) through us of opaque, sequentially numbered sealed envelopes (or an equivalent system, such as peelable stickers or scratch cards). In patients randomised to the intervention group, initial vascular access attempts will be via the intraosseous (IO) route. At least two attempts at vascular access via the intraosseous route will be made. The anatomical site of IO attempts will be at the discretion of the treating ambulance clinician. In making a decision as to site selection, the ambulance clinician will be mindful of contraindications to specific sites (e.g. fracture in target bone, prosthetic limb/ joint).

Once IO vascular access has been successfully achieved, cardiac arrest drugs (including fluid) will be administered through the IO cannula. Where clinically required, more than one IO cannula may be sited.

If the treating clinician has made two attempts at vascular access via the IO route and been unsuccessful at both attempts, then further attempts at vascular access may be made via the IO or IV route at the clinician’s discretion.

Where IO access fails at any point following successful insertion, further attempts at vascular access may be made via the IO or IV route at the clinician’s discretion.

Following return of spontaneous circulation, the treating clinician may choose to continue to use any established IO access or to insert an intravenous cannula.

In patients randomised to the control group, initial vascular access attempts will be via the intravenous route. At least

two attempts at vascular access via the intravenous route will be made. The anatomical site of IV attempts will be at the discretion of the treating paramedic. This reflects current NHS practice.

Once IV vascular access has been successfully achieved, cardiac arrest drugs (including fluid) will be administered through the IV cannula. Where clinically required, more than one IV cannula may be sited.

If the treating clinician has made two attempts at vascular access via the IV route and been unsuccessful at both attempts, then further attempts at vascular access may be made via the IO or IV route at the clinician's discretion.

Where IV access fails at any point following successful insertion, further attempts at vascular access may be made via the IO or IV route at the clinician's discretion.

CONSENT
The trial will recruit individuals that will be unconscious (having sustained a cardiac arrest) and who require time-critical treatment. On this basis, we plan to recruit individuals to the trial under a deferred consent model, in accordance with the Mental Capacity Act 2005. When patients regain capacity after being discharged from ICU, they will be approached to obtain consent. If the patient does not survive the cardiac arrest, relatives will be informed about their participants through passive methods to reduce the emotional burden during this distressing time.

DATA COLLECTION AND FOLLOW-UP
During this time information about their cardiac arrest and hospital stay will be collected from the patients hospital record by research paramedics. Information will also be obtained through data linkage sources. Long-term follow up will be conducted at 3 and 6 months following randomisation. Survival status will be obtained from NHS Digital or other electronic data sources. Quality of life questionnaires will be posted to the patient for completion at 3 and 6 months. They may be completed on the participant's behalf by someone that has a good awareness of their health state.

Follow-up for post discharge neurological outcomes and health related quality of life will be co-ordinated by ambulance services and follow an established system for contacting patients or their legal representatives ensuring effective follow up.

TIMETABLE FOR RESEARCH
The trial duration is schedule for 48 months with trial recruitment to take place over a 25 month period.

PLAN FOR INTERIM ANALYSIS/REPORT
The role of the Data Monitoring Committee and the Trial Steering committee will be to assess recruitment, the interim analyses in terms of the statistical monitoring.

SAMPLE SIZE
We will aim to recruit 15,000 patients to the trial.

PPI INVOLVEMENT
We have worked closely with patients and members of the public in designing the trial, including detailed discussions with our PPI co-applicant and presentation of the proposed trial to the Clinical Research Ambassador Group at University Hospitals Birmingham NHS Foundation Trial.

We will continue to embed meaningful patient and public involvement throughout the project, based on INVOLVE best practice guidance. We have convened a PPI group with a membership that reflects the diversity of people who are at risk of cardiac arrest. The PPI group will meet regularly throughout the trial. The group will support the development of patient and public facing information, advise on the strategy for approaching / informing patients about their participation in the trial, and advise on how we use information collected about people. The group will support development of a communication strategy (including social media), and support the dissemination of information to the public both during and at the end of the trial.

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?

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research

- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
We have worked closely with patients and members of the public in designing the trial, including detailed discussions with our PPI co-applicant and presentation of the proposed trial to the Clinical Research Ambassador Group at University Hospitals Birmingham NHS Foundation Trial.

We will continue to embed meaningful patient and public involvement throughout the project, based on INVOLVE best practice guidance. At the start of the trial, we will convene a PPI group with a membership that reflects the diversity of people who are at risk of cardiac arrest. The PPI group will meet regularly throughout the trial. Our named co-applicant PPI leads (Long/ Quinn) will be readily accessible to the group. The group will support the development of patient and public facing information, advise on the strategy for approaching / informing patients about their participation in the trial, and advise on how we use information collected about people. The group will support development of a communication strategy (including social media), and support the dissemination of information to the public both during and at the end of the trial.

We will identify at least two PPI members to become independent members of the Trial Steering Committee. This group will be responsible for the oversight of the trial and advising the Sponsor and Funder in accordance with the NIHR terms of reference for steering committees.

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

Please give details.
We plan to adopt the same approach used in the tested PARAMEDIC-2 study model. This model had significant input and agreement from dedicated patient, public and service user representatives.

For this trial, we explored the acceptability of our planned approach at the first meeting of our Patient Public Involvement panel, chaired by John Long (PPI co-applicant). The six-members panel includes individuals from a range of backgrounds and experiences, including cardiac arrest survivors, individuals with experience of critical illness, and others with experience through family members. The panel expressed their understanding regarding the purpose and reason behind collecting patient identifiable data without consent, and were supportive of planned approach. They expressed the justification and purpose for collecting this data without consent should be clearly explained in the patient information sheets and consent forms which the trial management group have ensured is included as per HRA and GDPR requirements.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [x] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [x] Generic Health Relevance

- [ ] Infection
- [ ] Inflammatory and Immune System
- [x] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	Years

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

1. Out-of-hospital cardiac arrest currently receiving cardiopulmonary resuscitation
2. Requirement for vascular access to administer cardiac arrest drugs

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

1. Children (known or appear to be < 18 years)
2. Known or apparent pregnancy
3. Already have vascular access

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
Eligibility assessment	1	0	<1 minute	Conducted by treating ambulance clinician at site of cardiac arrest
Randomisation	1	0	<1 minute	Conducted by treating ambulance clinician at site of cardiac arrest
Notification of enrolment and invitation to participate in follow-up (informed consent)	1	0	1-hour	Conducted by research paramedic- during hospital stay

Assessment of neurological outcome	3	0	5-minutes	Conducted by research paramedic- may be in-person, via telephone/ video call, or via web form
Completion of quality of life questionnaire (EQ-5D-5L) and health service use questionnaire	2	0	10-minutes	Conducted by research paramedic- may be in-person, via telephone/ video call, or via web form

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
Insertion of vascular access	1	1	1-minute	Conducted by treating ambulance clinician at site of cardiac arrest

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

○ Yes ◉ No

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

The study intervention will be used for the duration of the cardiac arrest and, where appropriate, the immediate post-resuscitation period. In most cases, this would be for a maximum of approximately one-hour.

Following randomisation, the participant will be followed-up for a period of 6-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.

Vascular access-
The insertion and use of both types of vascular access is associated with minor risks- these include infection, extravasation (misplacement of the needle and giving drug outside of the vein or bone marrow), and dislodgement. Additional risks specific to intravenous cannulation include phlebitis (vein inflammation), bleeding and accidental insertion of the needle in to an artery. Additional risks specific to intraosseous access are osteomyelitis (infection of the bone) and injury to the bicep tendon (if the needle is inserted in the upper arm).

These risks are minor, particularly in the context of a patient that has sustained a cardiac arrest.

Ambulance clinicians are trained and skilled in the insertion of both intraosseous and intravenous access. This includes following key procedures to minimise risk, including site cleaning, identifying anatomical landmarks to guide placement and checking for correct placement.

Follow-up-
Following cardiac arrest, patients may experience changes in their functional status (e.g. how far they can walk, ability to look after their own needs) or mental health (e.g. depression, anxiety). The completion of a health-related quality of

life tool may cause participants to reflect on these changes and may cause some anxiety. For face-to-face assessments (in-person/ video-call/ phone-call), research paramedics are skilled in conducting research follow-up and able to recognise signs of anxiety or distress. Immediate support may be provided by the research paramedic, who will (if needed) signpost the participant to other support services. On patient-facing follow-up surveys, we will include information on where additional support can be sought if needed.

Overall risk-
The basis for this trial is our hypothesis that an intraosseous vascular access strategy may facilitate earlier drug administration and thereby improve patient outcome.

The trial will be overseen by a Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) appointed by the National Institute for Health Research. At least 75% of the TSC will be independent from the study investigators. All DMC members will be independent of study investigators.

The TSC will provide overall trial supervision on behalf of the trial sponsor and funder, and ensure it is conducted in accordance with regulatory requirements and Good Clinical Practice.

The Data Monitoring Committee (DMC) will monitor safety in this trial. We will regularly prepare reports for the DMC, at an interval to be determined by the DMC. The DMC will determine the nature of any early stopping rules.

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:

As described in question A22, some patients experience changes in their physical and mental health following a cardiac arrest. In some cases, these changes will last a few weeks, whilst others will experience issues for the rest of their life.

Research paramedics conducting follow-up are experienced in this type of follow-up. In the event that a participant becomes distressed, immediate support may be provided by the research paramedic. If needed, the research paramedic will signpost the participant to other support services. On patient-facing follow-up surveys, we will include information on where additional support can be sought if needed.

Due to the nature of the follow-up, 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?

For participants randomised to an intraosseous access first strategy, individuals may benefit from earlier vascular access and drug administration. This may reduce the duration of the cardiac arrest and improve both survival and recovery.

For participants randomised to an intravenous access first strategy (current NHS standard of care), participants may benefit from improved drug availability as some evidence suggests drugs given intravenously may be more effective and have a faster onset.

Trial participation will provide important information about the most effective way to treat patients that sustain an out-of-hospital cardiac arrest in the future, both in the UK and across the world.

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- Individual participants will receive use of the allocated vascular access strategy only during the cardiac arrest itself and immediate post-resuscitation phase (in patients whose heart can be restarted).

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

Most trial participants will unfortunately not survive. This can be emotionally challenging for researchers, and may lead to stress and anxiety. Through previous trials in cardiac arrest, we have promoted a culture of openness that encourage discussion and sharing. Where needed, individuals (at both the University of Warwick and Ambulance Trusts) have access to counselling and other psychological support through occupational health departments.

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 that sustain an out-of-hospital cardiac arrest will be enrolled in to the trial by the treating ambulance clinician.

On arrival at the scene, the treating ambulance clinician will assess patient eligibility and, where appropriate, randomise the patient to enter the trial.

Individual ambulance services will develop systems for notifying research paramedics and the trial co-ordinating centre (Warwick Clinical Trials Unit) about enrolment.

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?

In participants that survive, we will we approach the participant or their consultee as soon as is practical and reasonable after the cardiac arrest event. From our experience of the PARAMEDIC AND PARAMEDIC 2 trials, following cardiac arrest many participants will require admission to an intensive care unit and be sedated to facilitate invasive mechanical ventilation. As such, the participant will continue to lack capacity. in this period, an approach to the participant's family is likely to be unduly burdensome, particularly given that there will be no ongoing trial intervention. On this basis, we anticipate that the first attempt to contact the patient and inform them of their enrolment into the trial will be during their stay in hospital at around the time of discharge from an intensive care unit to an acute hospital ward.

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.

If the participant has mental capacity to make a decision about ongoing trial participation, the ambulance service

researcher will approach the participant at an appropriate time to discuss ongoing study participation. The researcher will provide verbal information about the trial, as well as the written information sheet. The participant will be given adequate time to review the written information sheet and given the opportunity to ask questions. The participant's consent to the collection of patient reported outcome measures will be recorded on a signed consent form, counter-signed by the researcher.

If the patient is physically incapable of completing the consent form or where there are concerns regarding risk of infection transmission (i.e. due to the COVID-19 pandemic), verbal consent only will be sought from the patient and documented on a study form and in the patient hospital records by the person taking consent.

If the participant decides that it is not an appropriate time to discuss ongoing trial participation, the researcher will arrange a repeat visit at a more suitable time.
Participants may lack capacity following the cardiac arrest event. This may be temporary or permanent.

If the participant lacks mental capacity to make a decision about ongoing trial participation, the ambulance service researcher will work with the hospital team to identify and approach a personal consultee that meets the criteria described in the Mental Capacity Act 2005. The researcher will provide verbal information about the trial, as well as the written information sheet. The consultee will be given adequate time to review the written information sheet and given the opportunity to ask questions. The consultee will be asked to consider what decision the participant is likely to have made if they had mental capacity. The consultee's agreement to the collection of patient reported outcome measures and complete questionnaires on behalf of the participant will be recorded on a signed consent form, counter-signed by the researcher.

Significant limitations have been placed on visitation of relatives due to the COVID-19 pandemic and therefore, a personal consultee may not be able to physically sign the consent form. In this situation, the personal consultee will be contacted via telephone or videoconference facilities where verbal consent only will be sought. This will be documented on a study form and in the patient hospital records by the person taking consent.

If no personal consultee is available, researchers will approach a professional consultee. The professional consultee will be a registered medical practitioner that is not directly connected with the trial. The same process, as described for the personal consultee, will be followed.

If an initial approach is made to a professional consultee and a personal consultee subsequently becomes available, then the opinion of the personal consultee should be sought. This will override any decision made by the professional consultee.

If an initial approach is made to a professional consultee or a personal consultee and the participant subsequently regains mental capacity prior to hospital discharge, then the participant's consent should be sought. This will override any decision made by the professional or personal consultee.

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

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 a cardiac arrest out of hospital is unpredictable. Within seconds of cardiac arrest a person becomes unconscious and thus incapacitated. It will not therefore be possible to obtain 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. In this setting it will not be practical to consult a carer or independent registered medical practitioner for surrogate consent without placing the potential participant at risk of harm from delaying treatment.

Once the initial emergency has passed, consent for continuation in the trial will be obtained from patients who survive

or a consultee if the patient lacks capacity and for continue use of patient identifiable data.

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

As per A30, due to the urgent need to initiate treatment and the context in which the trial will operate, we do not consider it practical or appropriate to consult a participant, personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk to those involved. We believe the only practical way to proceed is to use an emergency waiver of consent model.

Following enrolment, the participant or consultee will be approached by the research paramedic team in hospital post ICU discharge or after discharge if they were unable to contact them at this time. They will be given adequate time to read the patient information sheet and accompanying cover letter to inform the research paramedic if they wish to take part or do not want to be contacted further about their participation and/or for data collection to stop.

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?

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with national NIHR supported co-enrolment guidelines. There are many current examples of successful co-enrolment between UK critical care studies, facilitated by these guidelines.

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)*

We will provide alternative arrangements where possible, to facilitate enrolment of patients who might not adequately understand verbal explanations in English or who have special communication needs. The trial team will identify common second spoken languages in the UK to provide translated information sheets in these languages to participating ambulance services if needed. Local hospital interpreters and translator services can also be used by the site to assist with the discussion of the study, participant information sheets and consent forms.

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?

We will work with local Welsh sites experienced in recruiting patients to research in the acute hospital setting. Sites will be supported in any additional costs in preparing written translations of the PIS and consent documents. We will ask local sites to arrange the translations in accordance with the availability of GCP trained staff who will be available to be involved in the research process.

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?

Should there be any subsequent amendment to the final protocol, which might affect the patient's participation in the trial, then these will be discussed with the participant or their consultee and, if applicable, continuing consent will be obtained using an amended consent form.

If new or relevant information becomes available that suggests one or more trial methods for administering drugs to cardiac arrest patients is causing harm or is ineffective then this treatment will be stopped.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

◉ The participant would continue to be included in the study.

○ Not applicable – informed consent will not be sought from any participants in this research.

○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

Please complete Part B, Section 6, giving further information about arrangements for including adults unable to consent for themselves.

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
- ☐ Access to social care records by those outside the direct social care 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 (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☑ Laptop computers

Further details:
Warwick Clinical Trials Unit will be responsible for the monitoring of data collection. They will oversee data sharing with any other external organisations should this arise.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal identifying consent forms and demographic details will be held in research site files, which will be stored in locations which are restricted to research team access. Patient identifiable data will only be transmitted to Warwick Clinical Trials Unit from participating sites via a secure online web portal, designed by the WCTU Programming Team. Access to this online web portal will be restricted to authorised members of the research team, via individual logins and IP addresses. Identifiable data will be held in a separate table within the trial database so that access can be further restricted to only individuals who require it. Any paper forms with patient identifiable information will be held in secure locked filing cabinets within a restricted access area at participating centres.

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.*

All trial staff and investigators will adhere to General Data Protection Regulation (GDPR) and the Data Protection Act 2018. The University of Warwick is registered on the Data Protection Act Register. Access to patient's personal data will be limited to the trial staff, investigators and regulatory authorities. Databases will only be accessed by authorised personnel using individual user accounts. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant number, not by name. Only anonymised data will be available to statisticians for data analysis. Participants will not be identified in any trial reports or publications.

A39. Please specify whether identifiers will be held in the same database as the clinical data, or in a separate database and linked through a unique study or case number. *If held separately, please specify how and at what point the separation will occur. If held in the same database, will the identifiers be encrypted? If so, specify what will be encrypted and who will continue to have access.*

Patient identifiers will be held in the same database as the clinical data, but in a separate table linked through a unique study number. The trial database is encrypted and held on a secure server at the University of Warwick. Access to the table containing patient identifiable data will be restricted to members of the trial team who require access e.g. undertaking data linkage work and contacting patients for follow up.

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 members of the research team at participating sites, who may sit outside of the patient's direct care team, for screening, recruitment and data collection purposes. Personal data will then be entered onto the trial database via the online web portal, which will be accessed at the University of Warwick Clinical Trials Unit by members of the coordinating centre trial team. The data that will be collected, the purposes and who will have access to that data is specified in the Patient Information sheet. Statement confirming understanding of this is included in the Patient Information Sheet.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be analysed by statisticians at Warwick Clinical Trials Unit, University of Warwick.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Professor	Gavin	Perkins
Post	Chief Investigator / Warwick Clinical Trials Unit Director		
Qualifications	MB ChB, MD, FFIMC, FICM, FERC, FRCP, FMedSci		
Work Address	Warwick Clinical Trials Unit		
	Gibbet Hill Road		
	Coventry		
Post Code	CV4 7AL		

Work Email	g.d.perkins@warwick.ac.uk
Work Telephone	02476 150925
Fax	

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

If longer than 12 months, please justify:
Access to personal data at participating centres may be required for the purposes of sponsor audit or inspection by the regulatory authorities, and must be stored for a period of 10 years or longer if required as per WCTU Standard Operating Procedures. Please note patient identifiable data will be deleted as soon as possible once no longer required (i.e. once communication with patients/legal representatives and data linkage work is complete).

A44. For how long will you store research data generated by the study?

Years: 10
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

The local Principal Investigators will maintain all records and documents regarding the conduct of the study. These will be archived by the site for at least 10 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at the secure archive facilities used by WCTU. This archive shall include all trial databases and associated meta-data encryption codes. Only the trial research team will have authority to access this data if required. The records will be archived for at least 10 years from the close of the study.

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

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
For participants that complete follow-up, we will provide a gift voucher of £5 to reflect the participant's time contribution.

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 UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. 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.
We will prospectively register the trial with the ISCTRN registry (https://www.isrctn.com/).

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)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Our publications will report only aggregated data.

In the event that there are very few individuals in a specific category (e.g. <5) that might facilitate identification, we will combine with another category and report as a combined category. In the event that grouping categories is not clinically meaningful, we will report the number of participants in the category as <5, rather than the exact number. We anticipate that this will be unlikely due to the large sample size of the trial.

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.
On our participant information sheet, we will include details of our trial website address where individuals can find information on results once the trial is complete.

In addition, participants that agree to participate in follow-up will be provided with a summary of results (where they have opted-in to this on the consent form).

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] 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:
This research was funded by the NIHR Health Technology Assessment panel. As part of this process, the scientific quality was reviewed by the HTA board (including clinicians, methodologists, patient/ public representatives, statisticians, and health economists). The funder review also included assessment by external experts.

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:*

- [x] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] 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
	Professor	Ranjit	Lall
Department	Warwick Clinical Trials Unit		
Institution	University of Warwick		

Work Address	Gibbet Hill Campus Gibbet Hill Road
Post Code	CV4 7AL
Telephone	02476574649
Fax	
Mobile	
E-mail	r.lall@warwick.ac.uk

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

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

Survival at 30-days post randomisation.

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

Any return of spontaneous circulation (ROSC)

Time to ROSC

Survived event (sustained ROSC at hospital handover)

Survival to hospital discharge, 3 and 6 months

Neurological outcome (measured by modified Rankin Scale (mRS) at discharge, 3, and 6 months)

Health related quality of life (measured by EQ-5D-5L at 3 and 6 months)

Hospital length of stay

Critical 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: 15000
Total international sample size (including UK):
Total in European Economic Area:

Further details:
Participants will be randomised in a 1:1 ratio to either the intervention or control group. The sample size was based on a formal sample size calculation.

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.*

We based the sample size on data from the PARAMEDIC-2 study and other literature.

Based on data from the PARAMEDIC-2 study, earlier drug administration is associated with 30-day survival (increase in 0.7% for each minute reduction).

Based on a conservation, but important, difference in survival of 1% (3.2% to 4.2%, proportionally 31%)- we require 14,972 participants to detect this treatment difference with a two-sided significance level of 5% and power of 90%. Based on previous trials, we anticipate high follow-up (~99.9%) rates for the primary outcome, therefore we will recruit 15,000 participants.

A61. Will participants be allocated to groups at random?

◉ Yes ○ No

If yes, please give details of the intended method of randomisation:
Patients will be enrolled in to the trial by the attending ambulance service clinicians. The treating ambulance clinician will determine whether there is a requirement for vascular access to administer cardiac arrest drugs, at which point they will assess the patient's eligibility for trial participation.

Eligible patients will be randomised in a 1:1 ratio to either an IO first strategy (intervention) or IV first strategy (control) through use of opaque, sequentially numbered sealed envelopes (or an equivalent system, such as peelable stickers or scratch cards). We will allow variability in system across ambulance services to reflect differences in equipment carried and systems of working. Randomisation will use variable block size and be stratified by ambulance service.

At the point that the envelope (or equivalent) is opened, the patient will be categorised as being randomised for the intention-to-treat analysis.

The allocation sequence will be generated by the study statistician. The allocation will be inserted in each envelope (or equivalent) by individuals that do not form part of the core trial team member to ensure that the study allocation remains blinded to the WCTU core trial team.

All envelopes (or equivalent) will be identical in appearance, such that clinicians, patients and trial personnel will be unaware of the treatment allocation inside. The envelope (or equivalent) will be supplied to each ambulance service, in a central location and will be distributed from there to participating ambulance stations and vehicles.

A standard operating procedure will be developed for each ambulance service to describe the process for replacement and traceability of all randomisation envelopes.

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 statistical analysis will be by intention to treat amongst those randomised to the IO first strategy versus the IV first strategy. The study findings will be presented using CONSORT guidelines and the primary analysis will be intention to treat. The primary outcome of 30 days survival rate will be assessed using logistic regression model with adjustment for important covariates.

Secondary outcomes which are categorical will be analysed in a similar way (using logistic regression models) and continuous outcomes will be assessed using linear regression models. Results will be reported using odds ratio or mean difference with 95% confidence interval.

Compliance with the randomised intervention and protocol violations will be assessed and appropriate statistical methods, namely CACE (complier average causal effect) and per protocol, will be used to assess the impact of deviation from the protocol. In addition, patients withdrawn from the intervention arms will also be assessed and examined using chi-squared test.

Unplanned crossovers across the interventions will lead to contamination of the initial randomised intervention due to a mixing of effects in the outcomes, reducing the power of the study. This is further complicated by the fact that crossover are often a very selective process whereby patients who have their treatment switched have a different prognosis that those who do not. We will work with ambulance staff through the training/initiation site set-up/monthly catch meetings to trouble shoot issues related to unplanned cross-overs. Unplanned cross-overs will be assessed in the analysis in two ways: (i) impact on the statistical power of the study: due to the contamination effect in patients who cross-over from one intervention to another, there is likely to be a reduction in the study power. We will examine the loss of the power, using power curves and different degrees of cross-over, pivoted around the observed cross-over rates. We will assess this at the end of the pilot study as well as at each DMEC meeting; (ii) for the final analysis, we will use inverse probability censoring weighted (IPCW) analysis to account for selective/unplanned cross-overs, using the primary outcome measure.

Secondary (exploratory) analyses will be based on comparisons of (a) IO (humeral) versus IO (tibial); (b) IO (humeral) versus IV; (c) IO (tibial) versus IV using the outcomes. These comparisons will not powered in the study and therefore the emphasis will be based on 95% confidence intervals and point estimates, as opposed to formal tests and p-values. These analyses will be carried out, using logistic regression models for categorical outcomes, such as survival to 30 days (and other binary outcomes) and using linear regression models for continuous outcome data.

Our sub-group analyses will include the assessment of treatment effect (a) age; (b) witnessed cardiac arrest versus not witnessed; (c) bystander CPR versus no bystander CPR; (d) initial rhythm; (e) time of 999 call to ambulance

arrival; (f) aetiology of cardiac arrest (presumed cardiac versus non-cardiac). Pre-specified exploratory subgroup analyses will be analysed using interaction term (treatment x sub-group) in the statistical models and reported using 95% confidence intervals, as the trial is not powered to identify interactions.

We will plan formal interim analyses to assess early stopping either for efficacy or harm during the main trial, whilst maintaining the type I error rate of 5%. In terms of stopping rules, we recommend the following and these will be discussed with the Data Monitoring Committee. We anticipate that there will be two formal interim analyses - when approximately 10% (early monitoring) and 50% (mid-way monitoring) of the total patient data are available. The early monitoring will occur when 1530 patients have their data available, and this will allow us to detect 1.5 minute difference in the time from randomisation to the administration of the intervention, between the two groups (90% power, 5% type 1 error). Mid-way monitoring will occur when 7026 patients have available data – this will allow us to detect a difference of 0.7 minutes difference in the latter time interval between the two groups (90% power, 5% type 1 error).

For each DMEC meeting, we will provide a graphical display of the odds ratios of survival versus time-to-access, using fractional polynomial methods. The odds ratios will be derived from regression models with the interaction of timing x treatment (IO(tibial)/IO(humeral)/IV)) and the graphical plot will allow us to assess the odds of survival over time, for each of the interventions. We will present this plot with 95% confidence bands. For the formal interim analyses, we will use the O'Brien and Fleming boundaries, as these stopping boundaries will preserve the overall type I error rate of 5% and account for the fraction of data available as well as the unequal spacing in the interim analyses.

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
	Dr	Keith	Couper
Post Qualifications	Assistant Professor in Emergency and Critical Care		
Employer	University of Warwick		
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	Coventry		
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	Title	Forename/Initials	Surname
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	Title	Forename/Initials	Surname
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	Title	Forename/Initials	Surname
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	Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
Prof	Rachel	Fothergill

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	Title	Forename/Initials	Surname
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Post	Senior Research Fellow		
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	Title	Forename/Initials	Surname
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	Title	Forename/Initials	Surname
	Dr	Alison	Walker
Post	Medical Director		
Qualifications			
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Post Code	DY5 1LX		
Telephone			
Fax			
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Work Email	alison.walker@wmas.nhs.uk		

	Title	Forename/Initials	Surname
	Mr	John	Long
Post	Patient Public Involvement Representative		
Qualifications			
Employer			
Work Address	N/A		

Post Code	
Telephone	
Fax	
Mobile	
Work Email	To be contacted via Trial Manager

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University of Warwick
Given name	Carole
Family name	Harris
Address	Research and impact services, University House, Kirby Corner Road
Town/city	Coventry
Post code	CV4 8UW
Country	United Kingdom
Telephone	024 765 75733
Fax	
E-mail	sponsorship@warwwick.ac.uk

Legal representative for clinical investigation of medical device (studies involving Northern Ireland only)
Clinical Investigations of Medical Devices that take place in Northern Ireland must have a legal representative of the sponsor that is based in Northern Ireland or the EU

Contact person

Name of organisation	
Given name	
Family name	
Address	

Town/city
Post code
Country
Telephone
Fax
E-mail

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] 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	NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
Address	University of Southampton Alpha House, Enterprise Road Southampton
Post Code	S016 7NS
Telephone	
Fax	
Mobile	
Email	

Funding Application Status: (•) Secured ( ) In progress

Amount: £3,090,356.41

Duration
Years: 4
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
Health Technology Assessment Progamme

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

◯ Yes ◉ No

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
	Mr	Andy	Rosser
Organisation	West Midlands Ambulance Service University NHS Foundation Trust		
Address	Millenium Point, Waterfront Business Park		
	Waterfront Way, Brierly Hill		
	West Midlands		
Post Code	DY5 1LX		
Work Email	research@wmas.nhs.uk		
Telephone	01384 215555		
Fax			
Mobile			

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

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

West Midlands

For more information, please refer to the question specific guidance.

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

Planned start date: 01/05/2021
Planned end date: 30/04/2025
Total duration:
Years: 3 Months: 11 Days: 30

A71-1. Is this study?

◯ Single centre
◉ Multicentre

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

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

Total UK sites in study

Does this trial involve countries outside the EU?

◯ Yes ◯ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

[x] NHS organisations in England	10
[x] NHS organisations in Wales	1
[ ] NHS organisations in Scotland	
[ ] HSC organisations in Northern Ireland	
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Joint health and social care agencies (eg community mental health teams)	
[ ] Local authorities	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent (private or voluntary sector) organisations	
[ ] Educational establishments	
[ ] Independent research units	
[ ] Other (give details)	
Total UK sites in study:	11

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

◯ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

A Trial Monitoring Plan will be developed by the trial team and approved by the CI and a member of the QA team. A risk based proportionate approach will be outlined in the monitoring plan to facilitate remote and off-site monitoring if required. This will be developed through discussion with the trial sponsor and will take in to account the challenging circumstance in which this trial may operate because of the COVID-19 pandemic.

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 role of the Data Monitoring Committee and the Trial Steering committee will be to assess recruitment, the interim analyses in terms of the statistical monitoring, data completeness and integrity, compliance to intervention and deviations from protocol.

For each DMEC meeting, we will provide a graphical display of the odds ratios of survival versus time-to-access, using fractional polynomial methods. The odds ratios will be derived from regression models with the interaction of timing x treatment (IO(tibial)/IO(humeral)/IV)) and the graphical plot will allow us to assess the odds of survival over time, for each of the interventions. We will present this plot with 95% confidence bands. For the formal interim analyses, we will use the O'Brien and Fleming boundaries, as these stopping boundaries will preserve the overall type I error rate of 5% and account for the fraction of data available as well as the unequal spacing in the interim analyses.

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 will plan formal interim analyses to assess early stopping either for efficacy or harm during the main trial, whilst maintaining the type I error rate of 5%. In terms of stopping rules, we recommend the following and these will be discussed with the Data Monitoring Committee. We anticipate that there will be two formal interim analyses - when approximately 10% (early monitoring) and 50% (mid-way monitoring) of the total patient data are available. The early monitoring will occur when 1530 patients have their data available, and this will allow us to detect 1.5 minute difference in the time from randomisation to the administration of the intervention, between the two groups (90% power, 5% type 1 error). Mid-way monitoring will occur when 7026 patients have available data – this will allow us to detect a difference of 0.7 minutes difference in the latter time interval between the two groups (90% power, 5% type 1 error).

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 of Warwick has public and product liability insurance with a limit of indemnity of no less than £10m to cover negligent acts resulting in damage injury or death it is legally liable for subject to policy terms and conditions.

The University of Warwick has professional indemnity insurance with a limit of indemnity of no less than £2m to cover breaches of duty subject to policy terms and conditions.

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 of Warwick has public and product liability insurance with a limit of indemnity of no less than £10m to cover negligent acts resulting in damage injury or death it is legally liable for subject to policy terms and conditions.

The University of Warwick has professional indemnity insurance with a limit of indemnity of no less than £2m to cover breaches of duty subject to policy terms and conditions.

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)

The University of Warwick has public and product liability insurance with a limit of indemnity of no less than £10m to cover negligent acts resulting in damage injury or death it is legally liable for subject to policy terms and conditions.

The University of Warwick has professional indemnity insurance with a limit of indemnity of no less than £2m to cover breaches of duty subject to policy terms and conditions.

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

If Yes, please give details of the compensation policy:
Insurer: Newline
Policy number: WIBCLT18365
Clinical Trial Insurance Specific Trial Policy in accordance with ABPI guidelines

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

B. All research other than CTIMPs

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

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

Out-of-hospital cardiac arrest.

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

This trial will recruit cardiac arrest patients in an out-of-hospital setting. Out-of-hospital cardiac arrest is a sudden and unpredictable event that immediately renders the patient unconscious and mentally incapacitated. It is not possible to answer this research question in a population that has mental capacity.

Due to the time-critical nature of cardiac arrest treatment to maximise the likelihood of patient survival, it will not be reasonably practicable to consult either a personal or professional consultee about trial enrolment as this would distract the ambulance clinicians. Further to this, delays in randomisation caused by consultation will limit our ability to reliably answer our research question.

Our trial hypothesis is based on the concept that earlier administration of cardiac arrest drugs facilitated by an intraosseous vascular access strategy will improve patient survival from out-of-hospital cardiac arrest. Our previous work has shown that each one-minute delay in drug administration is associated with worse outcome. On this basis, any delay to seek agreement for participation from a consultee will also reduce the treatment effect observed in the trial, and limit study generalisability to the real-world setting.

The only practical way to proceed is to utilise a deferred consent model, approved by a Research Ethics Committee. We have carefully considered the framework for a deferred consent model, developed by the Health Research Authority and Davies et al.

B3. 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?

In participants that survive, we will we approach the participant or their consultee as soon as is practical and reasonable after the cardiac arrest event. This is likely to be around the time of discharge from an intensive care unit to an acute hospital ward.

The ambulance service researcher in liaison with the hospital team will assess the participant's mental capacity in relation to their ability to make a decision about ongoing trial participation.

Participating ambulance service research staff will be experienced and trained in consent procedures in an acute care environment to appropriately assess mental capacity. They will have up-to-date GCP training and knowledge of the patient's condition and treatment through liaison with the hospital team to assess the patient's capacity to give consent. Ongoing monitoring through visits to the patient and through remote communications will repeatedly consider the patients capacity to give consent for themselves.

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

◉ Yes ○ No

If Yes, please indicate the nature of this benefit. You may refer back to your answer to Question A24.

Please refer to question A24.

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

◉ Yes ○ No

If Yes, please explain how the research will achieve this:

PARAMEDIC-3 will provide high-quality evidence as to the optimum strategy for the optimum medication route in cardiac arrest. The trial results will directly inform clinical practice.

B6. Will the research 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. Highlight any risk, burden or discomfort specific to these participants and say what will be done to minimise it. You may refer back to your answers to Questions A22 and A23.

Please refer to questions A22 and A23.

Questions B7 and B8 apply to any participants recruited in England and Wales.

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research.

If the participant lacks mental capacity to make a decision about ongoing trial participation, the ambulance service researcher will work with the hospital team to identify and approach a personal consultee that meets the criteria described in the Mental Capacity Act 2005. The researcher will provide verbal information about the trial, as well as the written information sheet. The consultee will be given adequate time to review the written information sheet and given the opportunity to ask questions. The consultee will be asked to consider what decision the participant is likely to have made if they had mental capacity. The consultee's agreement to the collection of patient reported outcome measures and complete questionnaires on behalf of the participant will be recorded on a signed consent form, counter-signed by the researcher.

Significant limitations have been placed on visitation of relatives due to the COVID-19 pandemic and therefore, a personal consultee may not be able to physically sign the consent form. In this situation, the personal consultee will be contacted via telephone or videoconference facilities where verbal consent only will be sought. This will be documented on a study form and in the patient hospital records by the person taking consent.

If no personal consultee is available, researchers will approach a professional consultee. The professional consultee will be a registered medical practitioner that is not directly connected with the trial. The same process, as described for the personal consultee, will be followed.

If an initial approach is made to a professional consultee and a personal consultee subsequently becomes available, then the opinion of the personal consultee should be sought. This will override any decision made by the professional consultee.

If an initial approach is made to a professional consultee or a personal consultee and the participant subsequently regains mental capacity prior to hospital discharge, then the participant's consent should be sought. This will override any decision made by the professional or personal consultee.

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

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?

◉ Yes ○ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, 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 advice from a consultee as soon as practicable thereafter.

Out-of-hospital cardiac arrest is a sudden and unpredictable event that immediately renders the patient unconscious and mentally incapacitated. It is not possible to answer this research question in a population that has mental capacity.

Due to the time-critical nature of cardiac arrest treatment to maximise the likelihood of patient survival, it will not be reasonably practicable to consult either a personal or professional consultee about trial enrolment as this would distract the ambulance clinicians. Further to this, delays in randomisation caused by consultation will limit our ability to reliably answer our research question.

Further to this, most cardiac arrest occur in the home, so it is likely that a consultee will be present in many cases. However, a cardiac arrest is a sudden and catastrophic event. Prior to ambulance arrival, the consultee is likely to have been instructed to deliver cardiopulmonary resuscitation which is physically exhausting. The combination of the likely overwhelming emotional response to the event and the physical exhaustion means that, in many cases, the consultee is likely to themselves lack capacity.

It is also not possible to consult with a professional consultee prior to starting urgent treatment as most out-of-hospital cardiac arrests in the UK are not routinely attended by a registered medical practitioner. In the unusual case that a registered medical practitioner is present, they are:

i. Unlikely to be independent as we intend to train all ambulance staff in trial processes,
ii. Any consultation would delay randomisation and distract attending ambulance clinicians from delivery of time-critical life-saving interventions.

On this basis, it will not be practical to consult a professional consultee.

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

PATIENTS THAT SURVIVE
In participants who survive, we will we approach the participant or their consultee as soon as is practical and reasonable after the cardiac arrest event. Following cardiac arrest, many participants will require admission to an intensive care unit and be sedated to facilitate invasive mechanical ventilation. As such, the participant will continue to lack capacity. In this period, an approach to the participant's family is likely to be unduly burdensome, particularly given that there will be no ongoing trial intervention. On this basis, we anticipate that the first attempt to contact the patient and inform them of their enrolment into the trial will be during their stay in hospital at around the time of discharge from an intensive care unit to an acute hospital ward.

At the point that an approach is considered practical and reasonable, the ambulance service researcher or hospital team will assess the participant's mental capacity in relation to their ability to make a decision about ongoing trial participation. Where an approach is led by an ambulance service researcher, they will first contact the hospital staff and confirm the participant's (or their consultee's) willingness to speak with them.

When an approach is made, the trial intervention will have been completed. The approach may be made in-person, by telephone, or via videoconferencing depending on participant preference, local policy, and equipment availability. The researcher will inform the participant (or their consultee) of their enrolment and explain that the focus of the consent process relates to ongoing participation, namely the collection of patient reported outcome measures through questionnaires. When we approach participants, we will supply them with a trial pen to keep, where this is available, as this has been shown to reduce attrition in those that consent We plan to continue to use routine health data sources for data collection unless the participant or their consultee explicitly refuses agreement for this use of data.

PATIENTS THAT DO NOT SURVIVE
Outcome following out-of-hospital cardiac arrest is poor despite the best efforts of members of the community, ambulance services, and hospital clinicians. It is possible to restart the patient's heart in approximately only 26% of cases and only 8% survive to leave hospital. In this trial, we plan to recruit a population of out-of-hospital cardiac arrest patients with a hospital survival rate of less than 5% (higher survival rates are seen among patients who achieve ROSC early and therefore do not require drug treatment).

Cardiac arrest is a sudden and unexpected event, such that the death may be particularly distressing for the patient's loved ones. On this basis, there is a need to carefully determine how, and if, we inform the loved ones of participants who die before either the family member or participant is informed about trial participation.

At the point of death, the trial intervention will have been implemented and no further active follow-up will occur. There is no legal basis for seeking consent/ agreement in this situation. The purpose of any communication with the participant's loved ones would be to inform them about trial involvement. On the one hand, providing information about trial participation ensures the trial recruitment is open and transparent, and it reduces the likelihood that family members will inadvertently find out about trial participation at a later date. On the other hand, knowledge about trial participation may place additional emotional burden on the participant's loved one at a time of already heightened emotional distress due to the loss of their relative or friend.

To address this, we will adopt the strategy used for the PARAMEDIC-2 trial that sought to carefully balance the need for transparency with the need to minimise the distress of the participant's loved ones. As such, we will adopt a strategy of providing passive information, whereby trial information is made publicly available (e.g. websites, newsletters) and locations likely to be attended by relatives of the deceased (e.g. hospitals, GP surgeries, Registrar of Births and Deaths offices, libraries, council websites). Such information would contain brief details about the study and a contact telephone number and address for further information. This approach enables individuals to make a choice about whether they wish to seek further information and the timing of that approach. A key disadvantage is uncertainty as to whether the loved ones of all participants will see this information. This approach, however, has been widely used across previous UK emergency care research.

We have discussed this in detail with our clinical ethicist and patient representatives who support this approach.

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

Following enrolment and discharge from ICU in hospital, the participant will be followed up by the ambulance service research and hospital team. In participants that regain capacity, the researcher will provide verbal information about the trial, as well as the written information sheet. The participant will be given adequate time to review the written information sheet and given the opportunity to ask questions. The participant's consent to the collection of patient reported outcome measures will be recorded on a signed consent form, counter-signed by the researcher.

If the patient is physically incapable of completing the consent form or where there are concerns regarding risk of infection transmission (i.e. due to the COVID-19 pandemic), verbal consent only will be sought from the patient and documented on the consultee consent form and in the patient hospital records by the person taking consent.

If the participant decides that it is not an appropriate time to discuss ongoing trial participation, the researcher will arrange a repeat visit at a more suitable time.

In the rare circumstance where participant consent is not obtained prior to hospital discharge, the ambulance service researcher will endeavour to contact the hospital team to understand the patient's condition prior to discharge. Where possible, the initial contact attempt will be made by post followed up by a phone call.

In the event that a trial participant declines consent to continue in the trial, personal identifiable data will be deleted. Information collected about the participant up to the point of withdrawal will be retained for analysis.

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

Following cardiac arrest, many participants will require admission to an intensive care unit and be sedated to facilitate invasive mechanical ventilation. As such, the participant will continue to lack capacity. Around the time of discharge from intensive care to an acute hospital ward, we anticipate the patient would have regain mental capacity.

Mental capacity will be assessed on an ongoing basis by the ambulance service research teams in liaison with the hospital team to determine the appropriate time to approach the patient and if a consultee should be used if the participant continues to lack mental capacity.

B12-1. What will be the criteria for withdrawal of participants?

Participants that are randomised, but subsequently found to be ineligible, will be included in the study analysis and all follow-up completed.

Participants or consultees on their behalf may request to withdraw from the trial at any time without prejudice. We will record details of participants that do not consent to the collection of patient-reported outcome measures. We will continue to collect routine health data sources for data collection unless the participant or their consultee explicitly refuses agreement for this use of data. The information sheet explains the trial and the data that will be collected.

In the rare case where researchers have been unable to make contact with a participant or their consultee following enrolment, we will continue to use routine health data sources for data collection.

B12-2. Where a participant is recruited urgently, and later withholds their consent or is withdrawn or dies before consent / consultation can take place, what provisions will apply to the study data collected up to that point?

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, data will continue be collected and submitted to Warwick Clinical Trials Unit. We will obtain approval from the Health Research Authority Confidentiality Advisory Group (CAG) to support the processing of identifiable data without consent. Study data will be linked to data linkage sources for data analysis purposes. Once data linkage has been completed, patient identifiers will be deleted.

In the event that the patient survives we plan to routinely collect patient identifiable data to facilitate data linkage otherwise there is a risk of introducing bias in to the study results. Our consent process if focused on the data collection of patient-reported outcomes. Where a participant does not consent to completion of patient reported outcomes or we are unable to contact the participant we will continue to collect and process personal identifiable data to facilitate data linkage unless the participant has explicitly withdrawn. If they choose to withdraw from the study, we would retain and use anonymised information collected up until that point.

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

At the time of the cardiac arrest, the participant will be unconscious and lack mental capacity to object to the trial intervention. When an initial approach is made by the ambulance service research team after discharge from ICU in hospital, the trial intervention has been completed. The focus of the approach will be to provide participants with an information sheet and consent form to obtain their consent to the collection of patient reported outcome measures. We plan to continue to use routine health data sources for data collection unless the participant explicitly objects to the use of this data in which their wishes will be respected.

Patients whilst in hospital after their cardiac arrest will continually be assessed by their clinical team as part of routine care, any signs of distress will be dealt with by the clinical team.

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?

It will not be possible to obtain knowledge of an advance decision or statement by the participant prior to randomisation and the trial intervention as a result of the nature of emergency setting the trial is performed in. However, GCP trained ambulance service researchers coupled with the local treating clinical team, will be obliged to identify the existence of any advance decisions or statements as part of consent considerations for ongoing patient reported outcomes. Any information in an advance decision or statement will be respected.

If the advanced decision is contrary to completing the study protocol and their continuation in the study would be contrary to their wishes, they would be withdrawn and all collected data discarded.

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 further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Jason
			Middle name	
			Family name	Wiles
	Organisation name	WEST MIDLANDS AMBULANCE SERVICE UNIVERSITY NHS FOUNDATION TRUST	Email	jason.wiles@wmas.nhs.uk
	Address	MILLENNIUM POINT	Qualification (MD...)	
		WATERFRONT BUSINESS PARK	Country	United Kingdom
		DUDLEY ROAD BRIERLEY HILL		
	Post Code	DY5 1LX		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Karl
			Middle name	
			Family name	Charlton
			Email	karl.chalrton@neas.nhs.uk
	Organisation name	NORTH EAST AMBULANCE SERVICE NHS FOUNDATION TRUST	Qualification (MD...)	MRes, Bsc Hons
	Address	BERNICIA HOUSE	Country	United Kingdom
		THE WATERFRONT		
		GOLDCREST WAY NEWCASTLE UPON TYNE		
	Post Code	NE15 8NY		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Rachael
			Middle name	
			Family name	Fothergill
	Organisation name	LONDON AMBULANCE SERVICE NHS TRUST	Email	rachael.fothergill1@nhs.net
	Address	220 WATERLOO ROAD	Qualification (MD...)	PhD, BSc
		LONDON	Country	United Kingdom

Post Code	SE1 8SD
Country	ENGLAND

IN7

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Nigel
Middle name	
Family name	Rees
Email	nigel.ress5@wales.nhs.uk
Organisation name	WELSH AMBULANCE SERVICES NHS TRUST
Qualification (MD...)	HCPC Registered Paramedic, PhD, MSc, BSc
Address	UNIT 7 FFORDD RICHARD DAVIES ST ASAPH BUSINESS PARK ST. ASAPH
Country	United Kingdom
Post Code	LL17 0LJ
Country	WALES

IN10

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Charles
Middle name	
Family name	Deakin
Email	charles.deakin@nhs.net
Organisation name	SOUTH CENTRAL AMBULANCE SERVICE NHS FOUNDATION TRUST
Qualification (MD...)	MA MD FRCA FRCP FFICM FERC
Address	7-8 TALISMAN BUSINESS CENTRE TALISMAN ROAD BICESTER
Country	United Kingdom
Post Code	OX26 6HR
Country	ENGLAND

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 fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. 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.

5. 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.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. 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.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. 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 2018.

10. 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.

11. 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 2018.

12. 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.

13. 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 Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

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

HRA 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 11/05/2021 15:21.

Job Title/Post:	Professor
Organisation:	University of Warwick
Email:	g.d.perkins@warwick.ac.uk

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 responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. 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.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mrs Carole Harris on 11/05/2021 15:58.

Job Title/Post:	Head of Research Governance
Organisation:	University of Warwick
Email:	sponsorship@warwick.ac.uk