PROTOCOL

Pre-hospitAl RAndomised trial of MEDICation route in out-of-hospital cardiac arrest (PARAMEDIC-3)

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TRIAL SUMMARY

Trial Title	Pre-hospitAl RAndomised trial of MEDICation route in out-of-hospital cardiac arrest (PARAMEDIC3)	
Internal ref. number (or short title)	PARAMEDIC-3	
Trial Design	Multi-centre, pragmatic, individually randomised, parallel group, superiority trial and economic evaluation	
Trial Participants	Adults (≥ 18-years) that have sustained an out-of-hospital cardiac arrest and who require vascular access	
Planned sample size	15,000	
Treatment Duration	Duration of cardiac arrest and immediate post-resuscitation period	
Follow-up Duration	6-months post-cardiac arrest	
Planned Trial Period	1st April 2021 to 31st March 2025	
	Objectives	Outcome Measures
Primary	To evaluate the effect of an IO first strategy on 30-day survival	30-day survival
Secondary	To evaluate the effect of an IO first strategy on other survival outcomes, neurological function, health-related quality of life, hospital length of stay, intensive care length of stay.	Return of spontaneous circulation; Survival (hospital discharge, 3-months, 6-months); neurological function (hospital discharge, 3-months, 6-months); health-related-quality of life (3-months, 6-months), hospital length of stay, intensive care length of stay.

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse event
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good clinical practice
ICF	Informed Consent Form
IO	Intraosseous
IPCW	Inverse probability censoring weighted
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
MID	Minimal important difference
MRC	Medical Research Council
PI	Principal Investigator
PPI	Patient & Public Involvement
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROLE	Recognition of life extinct
R&D	Research and Development
ROSC	Return of spontaneous circulation
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1 BACKGROUND

1.1 Epidemiology and burden of the condition

Each year over 30,000 people receive treatment from NHS Ambulance Services for an out-of-hospital cardiac arrest.(1) Within seconds of onset of cardiac arrest, consciousness is lost followed by tissue ischaemia, cellular injury, and death. Resuscitation measures achieve only 25-30% of normal cardiac output.

The time from cardiac arrest to achieving return of spontaneous circulation (ROSC) is a strong predictor of outcome.(2) For this reason, the NHS prioritises cardiac arrest for the fastest ambulance response and has developed systems to facilitate the delivery of key interventions such as cardiopulmonary resuscitation and defibrillation by members of the community before ambulance arrival.(3) Despite this, it is only possible to restart the patient's heart in approximately 26% cases and only 8% survive to leave hospital.(1) The NHS 10-year plan has prioritised improving cardiac arrest survival, with a commitment to saving an additional 4,000 lives a year.(4)

The use of drug therapy in cardiac arrest is supported by current clinical guidelines, both in patients that present in a shockable and non-shockable rhythm.(5, 6) Approximately 75% patients who sustain an out-of-hospital cardiac arrest receive drug therapy.(7)

1.2 Existing knowledge

Cardiac arrest drug treatments are effective in restarting the heart.(8, 9) The PARAMEDIC-2 trial showed that parenteral adrenaline, compared with placebo, is highly effective at restarting the heart (adjusted OR 3.83 (95% confidence internal (CI) 3.3-4.43), but has a much smaller effect on long-term survival (OR 1.39 (95% CI 1.06-1.82) and favourable neurological function (1.18 (0.86-1.61). In PARAMEDIC-2, drug treatments were administered on average 21 minutes after cardiac arrest. By this time, irreversible brain damage is likely to have already occurred. Modelling data from PARAMEDIC-2 shows that for every one-minute reduction in time to drug administration from ambulance arrival would increase absolute 30-day survival by 0.7% (22% relative increase).(10)

Current clinical guidelines recommend that cardiac arrest drugs are administered through the intravenous (IV) route, wherever possible.(5) However, peripheral IV cannulation is very challenging during out-of-hospital cardiac arrest due to both patient (e.g. veins collapsed) and environmental (e.g. sub-optimal positioning, poor lighting) issues. IV vascular access is successfully achieved at the first attempt in only around 50% of cases.(11) Repeated attempts at IV cannulation delays time to drug administration and distracts the limited resuscitation team from other key tasks.

In cases where intravenous vascular access cannot be rapidly achieved, clinical guidelines support use of intraosseous (IO) access, whereby a needle is sited in the bone marrow.(5) The most commonly used sites are the proximal humerus and proximal tibia.(11) Animal studies show that cardiac arrest drugs administered via the IO route reach the systemic circulation during cardiac arrest.(12-14) Pharmacokinetic studies

show that, compared with peripheral IV administration, sternal and humeral IO administration delivered similar peak drug concentration and time to peak drug concentration,(15, 16) whilst tibial IO administration appeared less effective in some(15, 17) but not all studies.(12, 18) By contrast, the effect of IO drug administration on ROSC appears similar to the IV route in both hypovolaemic(14, 18) and ventricular fibrillation cardiac arrest models.(17, 19)

Data from both observational and randomised controlled trials show that intraosseous access is faster and more likely to be successful.(11, 20) An observational study of 2656 out-of-hospital cardiac arrests reported that IO access, compared with IV access, was associated with more rapid drug administration (IO: 5.0 min (95% CI 4.7-5.4) v IV: 8.8 min (95% CI 6.6-10.9), p<0.001).(20) In the only published randomised controlled trial comparing IV and IO access, 182 people were randomised to peripheral IV access, tibial IO access or humeral IO access.(11) The study did not report clinical outcomes, but showed that the tibial IO route provided the quickest and most successful strategy for vascular access.

A systematic review coordinated by the International Liaison Committee on Resuscitation Advanced Life Support Task Force reviewed data from six observational studies and two randomised trials that compared drug efficacy in IV and IO sub-groups.(21) The review authors evaluated evidence certainty as very low. There was substantial heterogeneity across studies due to differences in study population, type of exposure (e.g. IO/IV attempt or successful IO/IV placement), drugs administered, outcome and analysis strategy (unadjusted versus adjusted analyses). A key limitation of observational studies is the influence of resuscitation time bias, where poorer outcomes are associated with delays to any intervention, including drug administration.(22). This is highlighted by a recent study, where an unadjusted analysis showed IO access to be associated with worse outcome, but a propensity score adjusted analysis reported comparable outcomes across the IO and IV groups.(23)

Secondary analysis of randomised trials mitigates the risk of resuscitation time bias as the difference in time taken to obtain vascular access by different routes should be evenly balanced between those receiving drug versus placebo. The ALPS trial, comparing Amiodarone, Lidocaine, Placebo, did not find evidence of an interaction according to route of drug administration.(8, 24) In the PARAMEDIC-2, the IO route was used in one third of patients, who were older, more likely to be in a non-shockable rhythm with drugs administered 3.9 minutes later (95% CI 3.3 to 4.5).(25) Despite these baseline imbalances, the odds ratios (adrenaline versus placebo) for ROSC at hospital handover were similar in the IV (aOR 4.07 (95% CI 3.42-4.85) and IO groups (aOR 3.98 (95% CI 2.86-5.53) with a p-value for interaction of 0.96. The confidence intervals for survival (discharge and 30 days) and favourable neurological outcomes for IV and IO similarly overlapped, with no statistical evidence of an interaction.

1.3 Research question

In adult out-of-hospital cardiac arrest patients, is an intraosseous access first strategy, compared with an intravenous access first strategy, clinically and cost-effective?

1.4 Need for a trial

There is widespread interest in the use of intraosseous drug administration in cardiac arrest. In the UK, there is evidence of changing clinical practice. Data on file from the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry show use of the IO route doubled over four-years (16% 2014 to 33% in 2018). This is consistent with data from London Ambulance Service which found that expenditure on IO equipment doubled over two-years (£177k in 2017 to £ 364k in 2019). Data from North America shows large variability in IO use, with IO use ranging from 1 to 53% across study sites participating in the ALPS trial.(24)

Published data suggest the IO route may be equivalent in efficacy to the IV route. In view of a higher insertion success rate and reduced time to obtain vascular access with the IO route, it is possible that an IO first strategy may translate to improved patient outcomes. However, some studies suggest the IO route may be inferior to the IV route, leading to reduced plasma drug concentrations(15) and an overall reduction in survival.(26, 27)

Registered clinical trials in Singapore (NCT02088736), China (NCT04130984), Taiwan (NCT04135547) and Poland (NCT02305511) of IO use in OHCA do not resolve this uncertainty for the NHS because: (i) health care systems differ; (ii) the trials do not test an IO first strategy; and (iii) the sample sizes are too small to provide a definitive answer.

In view of this ongoing uncertainty, the International Liaison Committee on Resuscitation, whilst continuing to suggest an IV first strategy, has highlighted the urgent need for a randomised controlled trial to determine the most effective approach.(5)

1.5 Ethical considerations

The trial will ensure that the rights, safety and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society.

This trial will recruit cardiac arrest patients in an out-of-hospital setting. Following onset of cardiac arrest, patients immediately become unconscious. Due to the time-critical nature of cardiac arrest treatment, it will not be reasonably practicable to consult either a personal or professional consultee about trial enrolment. On this basis, we plan to seek approval from a Research Ethics Committee to enrol trial participants without consent, in accordance with the Mental Capacity Act 2005. Following the emergency, we will discuss trial enrolment with the patient or their consultee at the earliest reasonably practicable opportunity. Our approach is guided by the framework for deferred consent in emergency research developed by Davies and colleagues in collaboration with the National Research Ethics Service.(28) Based on our experience in previous trials, we propose that, in general, a passive approach in relation to informing the relatives of participants that do not survive.

We considered developing a system to allow members of the public to request "no-trial" opt out bracelets. PARAMEDIC2 (a drug trial which compared adrenaline with placebo)

was to our knowledge the first trial and only trial to use this approach in the UK. We found a number of limitations to this approach which informed our decision not to provide this for PARAMEDIC3. Firstly, our experience was that checking for bracelets added complexity to the trial protocol (and potential delay to clinical treatments). Requests for bracelets often followed media stories, many of which contained factually incorrect information. The demographics of those requesting bracelets differed from those who sustain a cardiac arrest. None of the patients screened for enrolment in the trial were wearing a no-trial bracelet. The term opt-out, used by the media to describe the process, created confusion about legislation related to organ donation.

We also considered that PARAMEDIC3 differs from PARAMEDIC2 in a number of ways (1) it is testing one of two standard interventions currently used in the NHS (IV versus IO) (2) it is not a clinical trial of an investigational medicinal product and therefore falls under the Mental Capacity Act legislation. Consistent with the approach used in other emergency care trials which have enrolled people without capacity (e.g. PARAMEDIC, AIRWAYS2, RePHILL, CRASH) we reached consensus that the complexities and risk of including a system to opt-out outweighed the benefits.

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 framework for deferred consent in emergency research and University of Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with General Data Protection Regulation and Data Protection Act 2018.

1.6 CONSORT

The trial will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) statement.(29)

2 TRIAL DESIGN

2.1 Trial summary and flow diagram

We will conduct a multi-centre, pragmatic, individually randomised, parallel group, superiority trial with internal pilot and economic evaluation to determine the clinical and cost effectiveness of an intraosseous access first strategy, versus current NHS treatment.

Adult patients who sustain an out-of-hospital cardiac arrest that require vascular access will be randomised in a 1:1 ratio to either an intraosseous first strategy (intervention) or an intravenous first strategy (control) group. The control group reflects current NHS practice. Randomisation will occur at the point that a randomisation envelope (or equivalent) is opened.

The primary outcome will be survival at 30-days. Secondary outcomes include neurological function, quality of life, and survival at other time-points. Participants will be followed-up to six-months following cardiac arrest.

The trial will be conducted across English and Welsh ambulance services. A list of trial sites can be found on the trial website (https://warwick.ac.uk/fac/sci/med/research/ctu/trials/paramedic3)

A trial flow diagram is included as figure one.

2.2 Aims and objectives

2.2.1 Primary objective

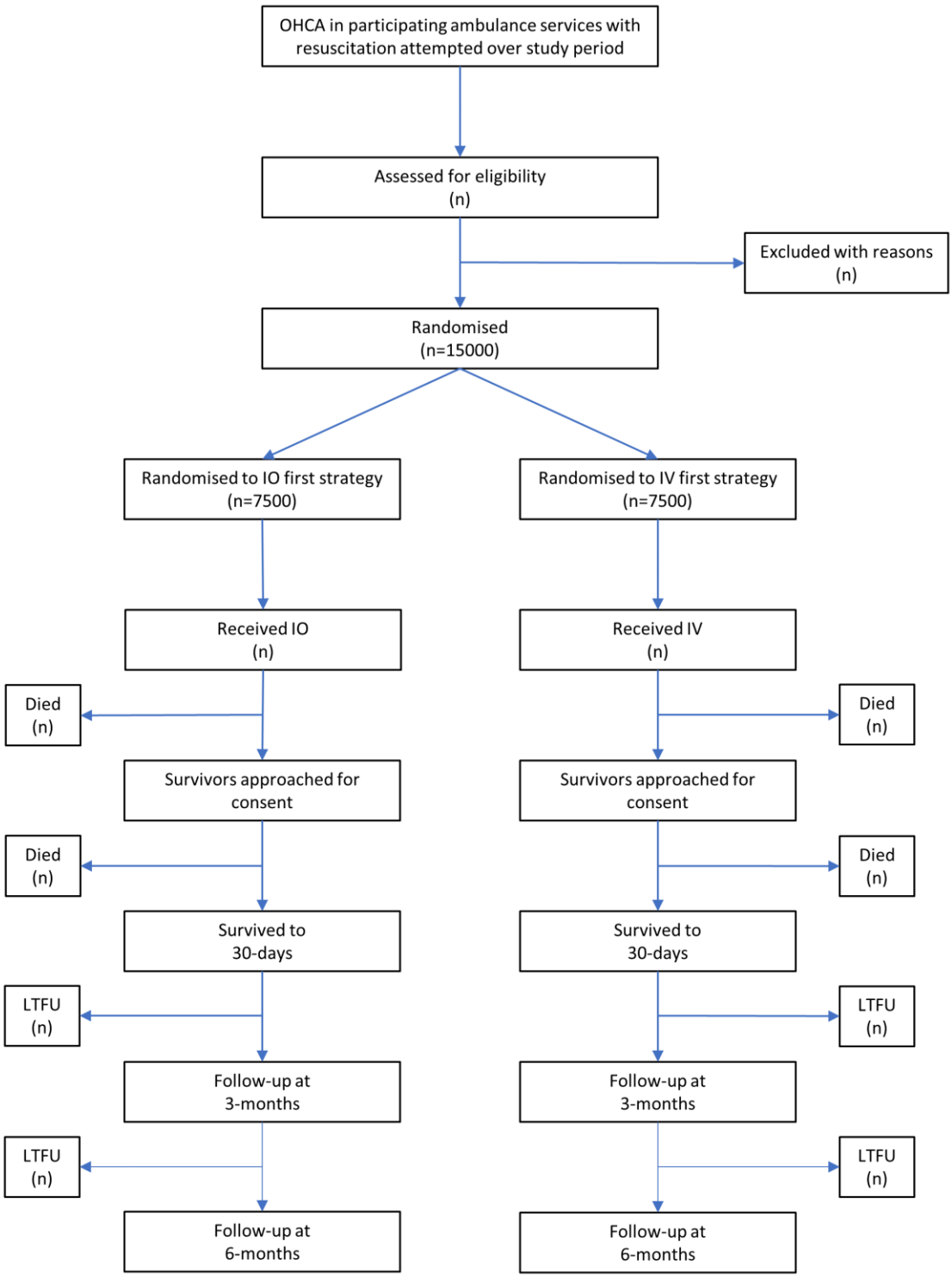
The primary objective of this trial is to evaluate the clinical effectiveness of intraosseous-first strategy in the treatment of OHCA, measured by our primary outcome of 30-day survival.

2.2.2 Secondary objective

Secondary trial objectives of the trial are:

1. To evaluate the effect of an IO first strategy on neurological function, quality of life and survival at other time-points.
2. To determine the cost-effectiveness of an IO first strategy.

Figure 1 **Trial flow diagram**



2.3 Outcome measures

Our chosen trial outcomes include long-term survival, favourable neurological function and health related quality of life, which were identified as core outcomes for cardiac arrest trials by the Core Outcome Set for Cardiac Arrest (COSCA) initiative.(30) We developed our chosen outcomes in collaboration with our patient and public collaborators.

Our primary outcome is survival at 30-days. Survival was chosen as our primary outcome because, in contrast to neurological function: it is less prone to attrition bias, it closely mirrors neurological function, and it is unlikely that the trial intervention will have differential effects on survival and neurological outcomes. Our time-point of 30-days was chosen as: it is sufficiently temporally separated from the peak of early deaths (which occur mostly in the first few days of intensive care(31)) to reflect long term survival, it avoids the effect that delayed discharges to social care may have on measuring survival to hospital discharge rates, and it is prioritised as a critical outcome for decision-making by guideline writing organisations. In PARAMEDIC-2, survival at 30-days was ascertainable in more than 99% of cases.(9)

2.3.1 Efficacy outcomes

The primary outcome is survival at 30-days

Secondary outcomes are:

- 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 function (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

2.3.2 Safety outcomes

Safety outcomes that fall outside of those reported as trial outcomes

2.3.3 Health economic

The primary health economic Incremental cost per quality-adjusted life year gained from the perspective of the NHS and personal social services.

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

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

2.4.2 Exclusion criteria

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

2.5 Participant identification / 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 is required. This will be immediately for patients in a non-shockable rhythm but may be delayed in patients in a shockable rhythm.

Once the need for vascular access has been determined, the ambulance clinician will assess the patient for eligibility. The eligibility criteria have been developed to facilitate a very rapid eligibility assessment. To determine eligibility, no additional tests or investigations are required. Should the clinician judge that either IV or IO access is in the best interest of the particular patient based on their clinical assessment of the situation they should select the relevant route and document the reason for exclusion. 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).

2.6 Site Staff Training

A programme of training will be provided to ambulance service clinicians responsible for trial recruitment. This will include the following: trial background; randomisation procedures; core principles of Good Clinical Practice; inclusion and exclusion criteria; data collection and documentation; and ethical issues and consent.

We will develop web-based training resources that enable clinicians to complete training at a time convenient to them. On completion of training, clinicians will complete an online form that will automatically notify both WCTU and the clinician's own ambulance service of training completion.

If it is more convenient to specific clinicians, training may be provided in person or via video conferencing. This training may be delivered by WCTU staff or by a member of ambulance service staff that has been approved to deliver training by the principal investigator.

Each ambulance service will maintain training records.

2.7 Informed consent

PARAMEDIC-3 will recruit individuals who 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.

2.7.1 Deferred consent and the Health Research Authority Framework

Out-of-hospital cardiac arrest is a sudden and unpredictable event that immediately renders the patient unconscious and mentally incapacitated. 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.

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 (table one).(28)

Table 1: Mental Capacity Act Consent Waiver framework (Davies et al (28))

1. Is this research needed?	Out-of-hospital cardiac arrest outcomes are poor. Drugs used to treat cardiac arrest are effective at restarting the heart, but often given late in the cardiac arrest. The time taken to restart the heart is associated with long-term outcome. The use of the intraosseous route to administer drugs in cardiac arrest potentially allows drugs to be administered earlier, thereby improving patient outcome.
2. Is there uncertainty about treatment?	A systematic review undertaken by the International Liaison Committee on Resuscitation identified very-low certainty evidence regarding vascular access route in cardiac arrest. In the UK, there is evidence of changing practice (increasing use of intraosseous access; increasing expenditure on intraosseous access). The International Liaison Committee on Resuscitation has stated the urgent need for research in this area.
3. Is there a need to recruit subjects who lack capacity?	Cardiac arrest causes an immediate loss of consciousness. It is not possible to answer this research question in a population that has mental capacity.
4. In the context of the research is consent or consultation feasible?	Cardiac arrest is a sudden and unpredictable event. Once cardiac arrest has occurred, the patient will immediately lose consciousness. It is not feasible to consult a personal consultee as: i. Consultation will distract ambulance clinicians from delivery of time-critical emergency treatment which will be harmful to the research participant;

	ii. Delays in randomisation caused by consultation will limit our ability to reliably answer our research question (see question 5).
5. Does treatment need to be given quickly? 6. Might delay change the effect of treatment or the results?	Cardiac arrest is a time-critical emergency. 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 reduce the treatment effect observed in the trial, and limit study generalisability to the real-world setting.
7. Will procedures accommodate variations in capacity?	Cardiac arrest causes an immediate loss of consciousness in all patients.
8. Would the legal representative/consultee be likely to have capacity?	Most cardiac arrests 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, may impair the consultees capacity. In addition, given the time critical nature of treatment for cardiac arrest, it is impractical for the paramedic to provide sufficient information and time to consider that information to allow a consultee to provide informed consent.
9. Is it practical to consult a professional legal representative unconnected to the research?	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.
10. What should the patient, consultee or	Due to the nature of the trial, the actual intervention period will continue only for the duration of the cardiac arrest event (often 20-30 minutes).

legal representative be asked later?	In survivors, we will seek consent from the patient or agreement their consultee for to complete patient-reported outcome measures, as detailed in section 2.7.2. We will undertake this consultation as soon as is practical and reasonable after the cardiac arrest event.

2.7.2 Participants who 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 pen to keep, where this is available, as this has been shown to reduce attrition in those that consent.(32) 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.

2.7.2.1 Participants with mental capacity

If the participant regains mental capacity to make a decision about ongoing trial participation, a 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 participant information sheet. An "easy-read" participant information sheet has been developed that provides key and targeted information about the trial. Where the "easy-read" participant information sheet is initially given, participants must still receive a copy of the standard information sheet. The participant will be given adequate time to review the 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. The consent form may be signed physically or, where this option is available, digitally.

If the patient is physically incapable of completing the consent form or where there are concerns regarding risk of infection transmission (e.g. due to the COVID-19 pandemic), verbal consent only will be sought from the participant and documented on a consent form. The researcher will annotate each box on the consent form to indicate consent to that item.

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

If required, translation services will be used to support the consent process. For common languages used in the UK, Warwick Clinical Trials Unit will provide translations of both information sheets and consent forms.

2.7.2.2 Participants who lack mental capacity

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 researcher will work with the hospital team to identify and approach a personal consultee who meets the criteria described in the Mental Capacity Act 2005. The researcher will provide verbal information about the trial, as well as the information sheet and cover note. The consultee will be given adequate time to review the 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 declaration form, counter-signed by the researcher. The declaration form may be signed physically or, where this option is available, digitally.

Significant limitations have been placed on visits by relatives because of the COVID-19 pandemic. Where an approach is made by telephone or videoconferencing and the opportunity is not available for a consultee to digitally sign the declaration form, then the researcher will document agreement on the consultee form, and the researcher will annotate each box to confirm consultee agreement.

If no personal consultee is available, researchers will approach a professional consultee who is not connected with the conduct of 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 opinion given 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 required, translation services will be used to support the consent process. For common languages used in the UK, Warwick Clinical Trials Unit will provide translations of both information sheets and consent forms.

2.7.2.3 Approaching patients or their consultee following discharge

In some circumstances, participant consent or personal/ professional consultee agreement may not be obtained before hospital discharge.

If this occurs, the researcher will contact the participant or their consultee (if it is known that the participant lacks mental capacity) at their home address to seek consent/ agreement. Where possible, the initial contact attempt will be made by post or email to allow time for the patient or consultee to consider their willingness to be contacted. This will be followed up by a phone call and second contact if no reply is received. Up to three contact attempts will be made within 28 days of the first contact. The researcher will use available systems (e.g. NHS Patient Demographic Service, liaison with primary/ secondary services, public access online systems) to ascertain correct contact information and, where appropriate, to ensure the participant is still alive. Where available, more than one system will be accessed to determine survival status

If the participant or their consultee does not respond to this contact within 28-days of the first contact, then we will assume that they do not agree to collection of patient-reported outcome measures. We will include data collected up to that point in the study analysis and we will continue to use routine health data sources for data collection.

2.7.3 Patients who 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.(1) 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).(9)

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, except for participants who are also enrolled in the POSED study. 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.

The strategy of actively informing participant's relatives about study enrolment is being trialled by the POSED study (Prehospital Optimal Shock Energy for Defibrillation; IRAS 277693; ISRCTN16327029). POSED will recruit 90 participants in the areas served by South Central Ambulance Service NHS Foundation Trust. For participants co-enrolled in PARAMEDIC-3 and POSED, we will adopt an active information strategy. A letter of condolence informing the participant's loved ones about their enrolment in both PARAMEDIC-3 and POSED will be sent approximately 4-6 weeks after the participant's death. The letter, whose wording was developed in collaboration with patient/ public representatives, will give individuals the opportunity to seek further information, either via a website or through discussion with the research team at South Central Ambulance Service NHS Foundation Trust. This will affect a small number of individuals (predicted to be 30-45).

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

2.7.4 Responsibilities

The Principal Investigator is responsible for ensuring that the consent processes described above are followed.

The consultation/ consent process will be undertaken by any appropriately trained researcher that has the approval of the site Principal Investigator.

2.8 Randomisation and post-randomisation withdrawals

2.8.1 Randomisation

Patients will be enrolled into the trial by an attending ambulance service clinician, who has received training in the trial protocol (see section 2.6). The 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, scratch cards or sealed treatment packs). 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). Members of the WCTU trial team maybe involved in this process. The risk of the trial team influencing the trial by having knowledge of allocation is considered to be extremely low as they will not have input into the distribution of envelopes within each ambulance service and cannot anticipate when randomisation events would occur. Once a randomisation occurs checks are made to ensure the received allocation is the same as the allocated intervention and cross-overs will be monitored by the TMG.

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.

2.8.2 Post-randomisation withdrawals and exclusions

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

We will record details of participants who 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.

2.9 Trial treatments / intervention

2.9.1 Intervention- Intraosseous first strategy

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 selecting a site, 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, except where local policy requires that specific specialist drugs are administered via the IV route. 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.

2.9.2 Control- Intravenous access first strategy

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 ambulance clinician. 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.

2.9.3 Risks of treatment

Both intraosseous and intravenous vascular access are routinely used across NHS practice. Key risks for both types of access include misplacement and dislodgement. Contraindications to both types of access relate to specific anatomical sites (e.g. evidence of local infection) rather than the patient. The key risks that are specific to

intraosseous vascular access are osteomyelitis. Very rarely injury to the bicep tendon may occur when the intraosseous needle is sited in the proximal humerus. Ambulance clinicians are trained in using both intraosseous and intravenous vascular access, including site selection, infection control procedures, and positioning of the arm to reduce the risk of bicep tendon injury.

2.9.4 Compliance/contamination

WCTU will monitor compliance using data reported by participating ambulance services. In the event of evidence of non-compliance, this will be flagged to the site research team. The site research team will then investigate events through discussion with the clinical team and, where appropriate, will report this as a protocol deviation. Where necessary, further training will be provided.

The descriptors of both the intervention (section 2.9.1) and control (section 2.9.2) mandate the use of a specific vascular access strategy only for the first two vascular attempts. If vascular access is unsuccessful after these first two attempts, then the treating clinician may decide which strategy is used for subsequent attempts.

2.10 Blinding

2.10.1 Methods for ensuring blinding

Due to the nature of the trial interventions, it is not possible to blind ambulance clinicians to treatment allocation. Hospital staff will be aware which intravascular access routes are in place upon hospital arrival but they will not be specifically briefed on the randomised allocation. We will limit the effect of knowledge of treatment allocation through the use of clinical protocols to guide treatments to reduce performance bias.

Participants will be initially unaware of treatment allocation by virtue of being unconscious during the resuscitation attempt. We will seek to reduce bias by not explicitly stating the treatment allocation.

2.10.2 Methods for unblinding the trial

Due to the open-label nature of the trial, there is no requirement for unblinding procedures.

2.11 Co-enrolment into other trials

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.

2.12 End of trial

The trial will end when all participants have completed their 6-month follow-up, receipt of routinely collected data, or the timepoint at which Confidentiality Advisory Group support is no longer required, whichever occurs later.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

2.13 End of trial for Confidentiality and Advisory Group (CAG) support

PARAMEDIC-3 has received Confidentiality Advisory Group support for the processing of confidential data without consent. The end of trial will be declared only once identifiable data held with support of CAG have been anonymised, such that CAG support is no longer needed.

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

3 METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table two summarises the trial schedule of events and data collection.

Table 2- Timing of routine trial assessments

Visit	1	2	3	4	5	6
Visit Window	Cardiac arrest	Hospital stay	Hospital discharge	30-days	3-months (± 1-month)	6-months (± 1-month)
Inclusion/exclusion criteria	✓	x	x	x	x	x
Randomisation	✓	x	x	x	x	x
Intervention	✓	x	x	x	x	x
Cardiac arrest data	✓	x	x	x	x	x
Patient identifiers	✓	✓	x	x	x	x
Safety reporting	✓	✓	✓	x	x	x
Hospital stay data	x	✓	x	x	x	x
Survival status	✓	✓	✓	✓	✓	✓

Neurological function (mRS)	x	x	✓	x	✓	✓
Notification of enrolment and invitation to participate in follow-up	x	✓	✓	✓	x	x
Informed consent*	x	✓	✓	x	x	x
Quality of life (EQ-5D-5L) and health resource use questionnaire	x	x	x	x	✓	✓
Check for national data opt-out		✓		x	x	x

*see section 2.7 for further details on the timings of seeking informed consent.

3.2 Long term follow-up assessments

Long-term follow-up will be conducted at 3-months and 6-months following randomisation. Survival status will be obtained from NHS Digital.

Follow-up questionnaires at 3-months and 6-months will usually be personally completed by the participant. This may be by postal questionnaire, face-to-face with a researcher, over the phone with a researcher, or via an online questionnaire. In the event that a participant is unable to complete the questionnaire (e.g. neurological deficit), it may be completed on the participant's behalf by someone that has a good awareness of their health state (e.g. relative/ carer). As a token of appreciation and to help improve follow-up rates, the participant will be provided with a £15 gift voucher alongside the 3 and 6-month questionnaire.(32)

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 (rates > 98%).(9, 33)

This system will include ambulance services conducting their own checks on the patients' survival using its own data systems, which will differ between services and may include accessing summary care records, contacting GPs or hospitals or consulting the NHS Patient Demographics Service.

To ensure ambulance services write to the correct address, they will confirm this with the patient where possible at the time of consent or check with the hospital, GP or public access online systems such as 192. After these checks, if someone is still believed to be alive the ambulance service will contact them at their home address as detailed above.

4 ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant participating in a clinical study and which does not necessarily have a causal relationship with the treatment/intervention.

4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Immediate intervention was required to prevent one of the above or is an important medical condition.

4.2 Assessing and Reporting AEs, SAEs and related SAEs

This trial is testing two interventions that are already used routinely in NHS clinical practice and will be used in line with their current market authorisation.

Events that are exempt from reporting due to their relationship to cardiac arrest patients undergoing attempted resuscitation rather than the intervention of the study **should not be reported** as either an adverse events or serious adverse event because they are collected as clinical outcomes. These include:

- Death
- Hospitalisation
- Persistent or significant disability or incapacity
- Organ failure
- Dislodgement / misplacement of vascular access
- Events related to the patients underlying disease or condition

Clinical details about these outcomes will be routinely collected in the case report form as part of the trial outcomes.

Events in patients undergoing attempted resuscitation **should be reported** unless it fulfils the exemption criteria above and it meets the two following criteria:

- It occurs between randomisation and hospital discharge.
- It is possibly related, probably related, or definitely related to the study interventions.

Reportable adverse events should be recorded on the case report form. Events that meet criteria for seriousness should be reported to WCTU Quality Assurance Team within 24-hours of becoming aware of the event.

Once a notifiable adverse event or serious adverse event has been identified, the participant should continue to be followed-up until resolution of the event or a final outcome has been reached. Following reporting of a serious adverse event, any change of condition or other follow-up information should be sent to the WCTU Quality Assurance team within 24 hours of the information becoming available.

The trial coordinator will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. All other recruiting sites in the trial will be informed of the event and any implications for the trial.

The causality of SAEs (i.e. relationship to trial intervention- see table three) will be assessed by the investigator(s) on the SAE form (see table three).

Table 3: Relationship of SAEs to trial intervention

Relationship to trial intervention	Description	Reportable in this trial
Unrelated	There is no evidence of any causal relationship	Not reportable
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Not reportable
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	Potentially reportable
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Potentially reportable
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Potentially reportable

All SAE reports will be reviewed on receipt by the Chief Investigator (or their delegate) for an independent causality assessment and those that are considered to satisfy the criteria for being possibly related, probably related or definitely related to trial interventions (either by the PI or CI) and which are not exempt from reporting will be assessed for expectedness by the CI or a clinical delegate at WCTU. SAEs that are deemed to be unexpected and related to the intervention will be notified to the REC and sponsor within 15 days of receipt in accordance with regulatory requirements. All such events will be reported to the Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings. Reports of all SAEs by randomisation arm will also be reviewed by the DMC at their regular meetings, or more frequently if requested by the DMC Chair.

4.3 Responsibilities

Principal Investigator (PI)/ delegate:

- Review participants (as per section 3.1) for adverse events:
- Using clinical judgement in assigning seriousness and causality.
- Ensuring that all reportable SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs are recorded and reported to the TMG in line with the requirements of the protocol.

Chief Investigator (CI)/ delegate:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
- Using clinical judgement in assigning causality
- Immediate review of all related and unexpected SAEs.
- Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Production and submission of annual reports to the relevant REC.

Sponsor/ delegate:

- Central data collection and verification of AEs, and SAEs, according to the trial protocol.
- Expectedness assessment of related SAEs
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of related and unexpected SAEs to the REC within required timelines.
- Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee (TSC):

- In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

- In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.4 Notification of deaths

Death is collected as a study outcome. No separate notification of death is required.

4.5 Procedures in case of pregnancy

Known or apparent pregnancy at the time of the cardiac arrest is an exclusion criterion for this trial.

Should a participant be randomised and later identified as having been pregnant at the time of randomisation, then the following will apply:

- Pregnancy itself is not regarded as an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject declined ongoing study participation.
- All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE.

4.6 Procedures in case of recruitment of an under 18 year old

Individuals who are known or apparently aged <18 years are not eligible for participation in the Paramedic3 trial. It is recognised that individuals that appear to be aged over 18-years may subsequently be identified as being aged under 18-years. In this scenario, if the participant survives, consent will be sought after the trial intervention from the participant (if aged 16 years or over) or from their parent or guardian (if aged under 16 years). For individuals aged 16 years or over, the standard consent process as detailed in section 2.7 will be followed.

If a participant under 16-years has capacity, they will be asked to provide assent for their continued participation in the trial. A Parent/ Guardian Consent Form and an Assent Form (for participants <16 years) will be provided for this purpose. Research staff may choose to use the “easy-read” information sheet to support the provision of information to individuals aged under 16-years.

Ambulance staff are skilled in the clinical care of individuals of all ages. However, we recognise that cardiac arrest in individuals under 18-years is a rare event, such that approaching individuals under 18-years for consent compared with approaching older individuals following cardiac arrest may be more emotionally challenging for ambulance service research staff. In the event that there is a need for a member of ambulance service research staff to approach an individual under 18 years, WCTU will work with the local site to provide any additional training or specific support required.

If the participant does not survive, data will be handled as for an individual aged 18-years or over.

4.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5 DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 2018 Data Protection Act and Warwick SOPs. Due to the need to link data across datasets, we will seek approval to hold confidential data without consent from the confidentiality advisory group.

Personal identifiable data will be held separately to trial data, with linkage provided through a unique trial number.

Ambulance services will cross-check each randomised participant to determine if they have opted-out of the use of their data for research purposes ('national data opt-out'). Ambulance services will be responsible for developing and implementing a process to determine the precise timing of these checks and method for notifying WCTU of 'opt-outs'. At the point that an individual has been identified as having 'opted-out', no further identifiable data will be collected until consent or consultee agreement can be obtained for data collection. If consent or consultee agreement cannot be obtained (e.g. in the case of death or refusal), any of the individual's identifiable data will be deleted by both ambulance service and WCTU. WCTU will confirm deletion of identifiable data to the ambulance service.
For patients that have "opted-out," ambulance service research staff will collect an anonymised dataset that incorporates the primary outcome. Participants who have opted-out will be included in the final analysis. We will apply this process to both participants that have already been randomised and those that are randomised in the future.

This process aligns with ambulance service research staff role in directly supporting patient care, thereby providing a common law basis for accessing information. The anonymised data set will be in line with the Information Commissioner's Office Code of Practice on Anonymisation.

5.1 Data collection and management

Data management processes will be documented in a Data Management Plan. To optimise trial efficiency and minimise data collection burden, we plan to use routine data sources, wherever possible, to collect data.

Data from ambulance services will be entered into the trial database, including personal identifiable information to allow data linkage. Personal identifiable data will be handled in accordance with relevant legislation and WCTU SOPs.

Key data sources include the out-of-hospital cardiac arrest outcome registry, NHS Digital, Hospital Episode Statistics, the Intensive Care National Audit and Research Centre (ICNARC) case-mix programme, Health Data Research UK, Patient Episode Database for Wales (PEDW), National Institute for Cardiovascular Outcomes Research (NICOR), ONS mortality data, GP records and the UK Transplant Registry (UKTR). These data sets will also be used for the health economic analysis and collection of some safety data.

These data sources will be supplemented by a case report form to capture information that is not currently recorded in these datasets. Case report forms will be completed by research paramedics, based on information in the clinical record or through discussion with the treating clinician. The case report forms (CRFs) and questionnaires will be designed by the trial manager in conjunction with the Chief Investigator, ambulance services and Statistician.

5.2 Screening and notification of trial enrolment

Sites will maintain a screening log to record all cardiac arrests, and reasons for not enrolling in to the trial. Ambulance service research staff will use the comprehensive systems we developed in the PARAMEDIC trials to interrogate call centre databases, computerized patient records and other sources to ensure that all cardiac arrests cases are captured to allow a comprehensive assessment of screening to recruitment rates.

Following randomisation, notification of trial enrolment will occur initially through the ambulance service clinical team. Following hand-over of care (or termination of resuscitation attempts), the treating ambulance clinician will notify the research paramedic of:

- Ambulance case number
- Unique trial number
- Destination (hospital name or non-transport (death)
- Ambulance crew identification number.

The ambulance clinician will also record the trial recruitment number, and record usage of a randomisation card on the clinical record.

Screening logs will be reviewed by the Trial Management Group, Trial Steering Committee and Data Monitoring Committee.

5.3 Hospital admission through to discharge

Ambulance service researchers will liaise with hospitals and use the NHS Spine to access the Summary Care Record as the primary method of checking patients' survival status, and facilitate an approach to discuss collection of patient-reported outcome measures.

5.4 Post discharge and long term follow-up

We will track mortality up to 6-months using electronic databases.

Patients who survive and give consent for follow-up will be contacted (either in-person or via video/ phone-call/electronic method/ post, depending on patient preference and ambulance service systems) at 3-months and 6-months by a member of the ambulance service research staff. At 3-months and 6-months neurological function (mRS), health-related quality of life (EQ-5D-5L) and resource utilisation (NHS and PSS, as well as broader resource utilisation) will be assessed.

5.5 Database

The database will be developed and tested by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

5.6 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.7 Data access and quality assurance

All data access will be controlled by individual usernames and passwords and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role and responsibilities in the study documented on the central coordinating delegation log. Any data that are transferred out of the secure environment (for example for statistical analysis, ICNARC, HES) will adhere to Warwick SOPs.

5.8 Data Shared with Third Parties

The trial statisticians and DMEC will have access to the dataset for the analysis of trial outcomes. Once the main analyses have been undertaken, deidentified individual participant data will be available to principal and other investigators subject to approval of data analysis plans by the TSC and compliance with the University of Warwick SOPs on Data Management and Sharing. We will comply with Data Sharing Policies that may be instituted by the NIHR during the lifetime of the project.

5.9 Archiving

Trial documentation and data held at Warwick Clinical Trials Unit will be archived for 10-years after completion of the trial. The trial master file and associated data will be archived by WCTU. Trial data generated at study sites will be archived for 10-years, anything longer than this would be in accordance with local policy.

6 STATISTICAL ANALYSIS

6.1 Power and sample size

In the PARAMEDIC-2 trial, the time from ambulance arrival to drug administration was 14.0 and 18.4 minutes for IV and IO patients, respectively. As illustrated above, by reducing the time to drug administration, the 30-day survival rate could be increased by 0.7% per minute.

The reduction in time to treatment administration by using IO varies from 1.0-6.2 minutes in the literature and this implies that we could have an increase in survival between 1.7%-5.2%, when comparing administration of drug with IV and IO.(11, 20)

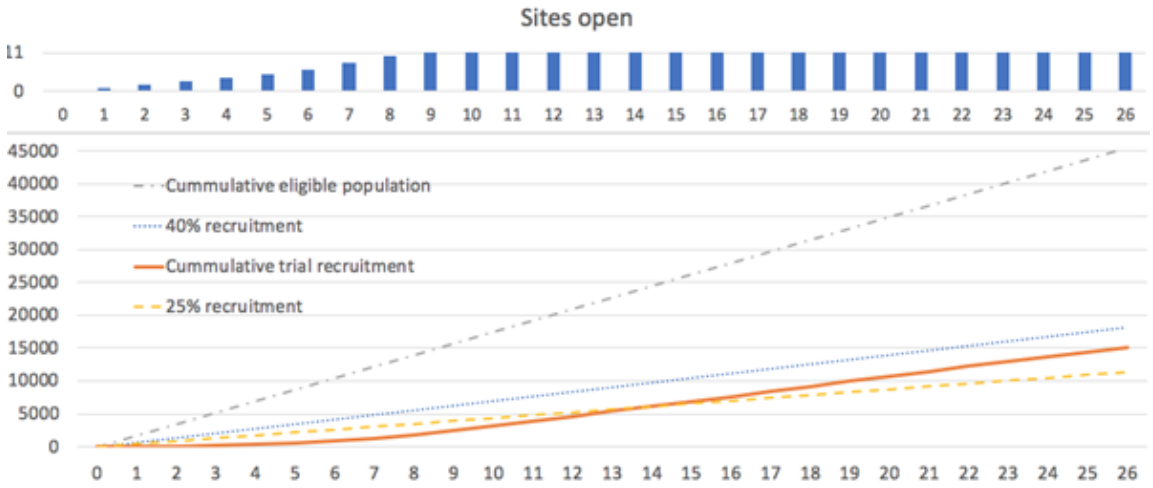
We propose a conservative but worthwhile difference in survival of 1% (3.2% to 4.2%, proportionally 31%). To detect this treatment difference with a two-sided significance level of 5% and power of 90%, we need data on 14,972 participants. Our experience in the PARAMEDIC trials (12k patients) indicates a very good follow-up rate of 99.9%. Therefore, we will recruit 15,000 participants.

We will assess the outcomes in the IO (humeral) and IO (tibial) routes as a hypothesis generating, secondary analysis (detailed below). We do not know how unequal this distribution will be, but if the allocation was equal (at best) then assuming 30-day survival in one of the arms ranges from 3.2%-5.2% (where the overall average of IO is 4.2%), then the minimal important difference (MID) that could be detected using the IO sample of 7500 would range from 1.5%-1.8% at 90% power. For a very unequal allocation, the MID would range from 1.8%-4.0%. A further comparison will be carried using one of the IO arms (tibial or humeral) versus IV, where there are 7500 patients on IV and 3750 (on one of the IOs), In this comparison if we compare IV (with a survival rate of 3.2%) vs one of the IO approach (arm or tibial), a minimal important clinical difference of 1.3% (at 90% power) using a total sample size of 11250 patients.

6.2 Statistical analysis of efficacy and harms

6.2.1 Planned recruitment rate

Recruitment has been modelled on the rates observed in PARAMEDIC-2 (65 patients per site per month) and AIRWAYS2 (89 patients per site per month). We have allowed for a staggered set up of sites and gradual increase in recruitment rates over time (initially 30 patients per site per month, increasing to 70 patients per site per month by the end of the trial). The figure below shows the total eligible population during recruitment to the trial and the numbers if 25% and 40% of the eligible population are recruited.



6.2.2 Primary outcome analysis

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.

6.2.3 Secondary outcome analysis

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 crossovers are often a very selective process whereby patients who have their treatment switched have a different prognosis than 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.

6.2.4 Subgroup analyses

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.

6.2.5 Interim analysis and criteria for the premature termination of the trial

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.

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.

6.2.6 Subject population

Data from the national cardiac arrest registry hosted at Warwick shows that approximately 50,000 patients sustain an OHCA each year in the UK. NHS Ambulance Services attempt resuscitation in approximately 30,000 patients. Those beyond resuscitation are declared deceased, based on the national recognition of life extinct (ROLE) criteria.

National (UK) resuscitation protocols require ambulance clinicians to start treatment initially with cardiopulmonary resuscitation (CPR). For patients in an initially shockable rhythm (ventricular fibrillation / pulseless ventricular tachycardia), defibrillation is attempted. Obtaining vascular access and administering drugs is prompted after three failed attempts at defibrillation OR, if the patient is in a non-shockable rhythm.

6.3 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, according to the recommendations of the NICE reference case.(34)

Resource use will be recorded, including intervention, hospital (ICU, HDU and ward days) and community costs (primary care and personal social services) in the first 6 months following randomisation. Healthcare resource use will be costed using most recently available published national reference costs, reflated to the most recent year.(35, 36) We will simplify resource collection as much as possible, preparing participants to understand the resource information sought and promoting this recording through diaries or calendars.

Generic health-related quality-of-life will be assessed at 3 months and 6 months using the EQ-5D-5L questionnaire. Baseline EQ-5D-5L values will be imputed to reflect the unconscious health state minimising potential bias in the QALY AUC calculation.(37, 38) EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis.(39, 40) Participant level QALY estimates will be estimated as the area-under-the-curve (AUC) of health status scores over time using the trapezoidal rule.

Within-trial analysis (to 6 months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost-effectiveness.(41) Mechanisms of missingness of data will be explored and multiple imputation methods will be applied if required to impute missing data.(42-44) Imputation sets will be used to estimate incremental cost per QALY estimates and confidence intervals. Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis (VOI).

Within-trial findings, reflecting the outcomes and prognosis of patients at 6 months, will inform a lifetime decision-analytic model. Modelling will draw upon best available information from the literature to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer term costs and consequences will be discounted to present values at 3.5% per annum in line with NICE reference case.(34) Sensitivity analyses will be undertaken to explore uncertainty and to consider issues of generalisability of the study.

Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.(45)

7 TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will act as trial sponsor. The trial will be conducted in accordance with Warwick Clinical Trial Unit Standard Operating procedures.

7.2 Ethical approval

We will request ethical approval for this study by a research ethics committee, flagged for studies involving adults lacking capacity. The required ethical approval for the trial will be sought using the Integrated Research Application System.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has been reviewed by the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of the approval via the HRA is received by the PARAMEDIC3 trial team, based at WCTU.

As the trial will recruit participants under a deferred consent model in accordance with the Mental Capacity Act 2005, we will additionally seek approval from the Health Research Authority Confidentiality Advisory Group (CAG) to support the processing of confidential data without consent.

We will submit annual reports to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. We will notify the REC and HRA of any amendments and at the point that the trial concludes and provide a final report in accordance with reporting requirements.

As part of the funding decision by the NIHR HTA, the trial was reviewed by both the HTA board and independent individuals with clinical, methodological, and patient involvement expertise. The trial is supported by the College of Paramedics, Joint Royal College Ambulance Liaison Committee, National Ambulance Research Steering Group, and Resuscitation Council UK.

7.3 Trial Registration

We will prospectively register the trial with an appropriate trial registry.

7.4 Notification of serious breaches to GCP and/or trial protocol

The management of non-compliances will be informed by Warwick Standard Operating Procedure 31.

7.4.1 Trial protocol deviation and violations

Non-compliance with clinical trial protocols and GCP occur commonly in clinical studies. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial.

Non-compliance will be categorised as a deviation, violation or serious breach by the trial management group according to the following definitions:

A deviation is a change or departure from the protocol, other key trial documents and/or GCP that does not result in harm to the participants or significantly affect the scientific value of the reported results of the study. Deviations are usually due to unavoidable circumstances or events that are planned due to clinical need. Protocol deviations will be summarised and reported to the trial management group and oversight committees.

A violation is a failure to comply with, or variance from, GCP and/or the final protocol or other key trial documents as approved by Sponsor, REC, MHRA (where applicable) and NHS Trust Research & Development (R&D) departments. It is also a variance from any

regulations or legislation relevant to the delivery of clinical research e.g. DPA/GDPR, Common Law Duty of Confidentiality etc. Violations are serious non-compliances resulting from error, fraud, or misconduct which have the potential to harm participants or significantly affect the scientific value of the reported results of the study. The WCTU QA team and Sponsor will be informed about protocol violations as soon as is practicable. Oversight committees will review trends identified across sites.

Protocol deviations or violations (and actions taken to prevent recurrence) will be recorded in the case report form. Serious breaches of the study protocol or GCP should be immediately reported to the Chief Investigator. The Chief Investigator in consultation with the PI will take whatever immediate action is required to safeguard the wellbeing of participant(s). The Chief Investigator will notify the Sponsor immediately and Ethics committee within 7 days of becoming aware of the serious breach.

7.4.2 Serious breach

A "serious breach" is a breach which is likely to effect to a significant degree –

1. the safety or physical or mental integrity of the subjects of the trial; or
2. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase, and will notify the licensing authority in writing of any serious breach of:

1. the conditions and principles of GCP in connection with that trial; or
2. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

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

7.6 Trial timetable and milestones

Total project duration is scheduled to be 48-months. A summary of key trial milestones is shown as table four.

Table 4: Project milestones

	Month	Recruitment
Set-up	1-6	-
Pilot study	7-12	840
Recruitment	13-32	14,160
Follow up and close-down	33-42	-
Analysis, reporting and dissemination	43-48	-

7.7 Administration

The trial co-ordination will be employed at WCTU, University of Warwick. All day-to-day coordination of the trial will be the responsibility of the Trial Manager. Clinical coordination of the trial will be the responsibility of the Chief Investigator. The trial is managed by a multi-disciplinary team.

The coordination team will assist and facilitate the setting up of centres wishing to collaborate in the study. In addition the coordination team will:

- Distribute access to the standardised data collection forms to collaborators
- Monitor the collection of data, process data and seek missing data
- Train local staff with regards to data collection remotely
- Ensure the confidentiality and security of all study forms and data
- Conduct extensive data checking and cleaning
- Organise any interim and main analyses
- Organise Steering Committee, DMC and Collaborators meetings

The study office will receive completed data forms, via the online web application, post or email. Upon receipt, data forms will be checked for completeness and entered into a study specific dedicated computer programme which will check the data validity.

7.8 Trial Management Group (TMG)

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

7.9 Trial Steering Committee (TSC)

A trial steering committee will be appointed by the funder.

The role of the TSC/SSC is to provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the project is the responsibility of the Chief Investigator, and as such the Chief Investigator may wish to set up a separate Project Management Group (PMG) to assist with this function.

The main responsibilities of the TSC are defined by the funder as follows:

- To provide advice, through its Chair, to the Trial Funder, the Trial Sponsor, the Chief Investigator, the Host Institution and the Contractor on all appropriate aspects of the project

- To concentrate on progress of the trial/project, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the trial/project.
- The membership of the TSC is shown on pages 4-5.

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

7.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet prior to the start of the trial and at intervals not less than annually thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on pages 4-5.

DMC meetings will also be attended by the Chief Investigator and trial manager (for non-confidential parts of the meeting, trial statistician and observers if deemed appropriate

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

7.11 Essential Documentation

A Trial Master File will be set up according to University of Warwick SOP and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7.12 Financial Support

This study is funded by the National Institute for Health Research (NIHR) HTA programme (NIHR131105). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

8 MONITORING, AUDIT AND INSPECTION

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.

8.1 Training

All ambulance clinicians participating in the trial will be trained at least once as detailed in section 2.10. It will not be possible or proportionate to fully train all clinicians in GCP. A risk adapted approach which focuses on the relevant general principles will be covered during the training.

Web-based training resources will be available to allow clinicians to complete training remotely at a time convenient to them. On completion of training, clinicians will complete an online form to automatically notify both WCTU and the clinician's own ambulance service of training completion.

In addition to completion of online training; Principal Investigators and ambulance service research staff will be required provide evidence of GCP training. WCTU will keep a record of the principal investigator's CV and GCP certificate. WCTU will monitor completion of online training for staff listed on the trial delegation log to ensure they are adequately trained to perform trial related activities.

Training will also be carried out for WCTU administration staff who may answer phone calls from patients or consultees and need to deal sensitively with their questions.

8.2 Data Quality

Data entered into the trial database will be checked for accuracy in accordance with the WCTU SOPs and trial Data Management Plan.

Quality assurance checks on eligibility, completion of data, follow up questionnaires and the consent process will ideally be carried out after the pilot period and each year of recruitment, but as this may pose logistical issues, the checks and any subsequent training will be carried out at least once during the recruitment period and as per the WCTU Data Management Plan.

Audits of routine ambulance service data will be performed by WCTU and ambulance services at regular intervals, to identify cardiac arrests and potentially eligible patients who were not reported to the trial.

8.3 Visits to Sites

As per the WCTU monitoring plan, the trial manager will have regular contact with the ambulance service trusts to identify any problems with compliance with the protocol, training, data collection or other barriers to recruitment and progress, and to support sites with the day to day management of the trial within the ambulance services trusts. As well as regular telephone and email contact, we plan to undertake at least one site

visit/remote visit (COVID-19 pandemic permitting) during the trial to meet with the trial team at each ambulance service, discuss any issues, and check for consistencies.

The Trial Manager will check with each ambulance service that all Site Master Files documents are up to date at least once during the trial.

9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

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.

A summary of patient and public involvement using the GRIPP2 framework will be included in the final study report.(46) In all patient and clinician facing materials, we will include a summary of how PPI members have been involved in the project.

10 DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The success of the trial depends on the collaboration of ambulance services from from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

We will publish the trial protocol and final trial results in high impact, open access peer reviewed journals.

We will work with the University of Warwick marketing and communication team to develop a strategy for communication with the media to enhance communication of the trial delivery and results to participants and members of the public.

We will develop a specific dissemination strategy for each of our key audiences- these strategies are likely to include:

- Clinicians- Open access publication in peer-reviewed journals (including HTA monograph), conference presentations, podcasts, and infographics.
- Policy makers- Open access publication in peer-reviewed journals (including HTA monograph), conference presentations, targeted communications at key national and international organisations (e.g. College of Paramedics, Resuscitation Council UK, European Resuscitation Council, American Heart Association, National Association of Ambulance Medical Directors, and International Liaison Committee on Resuscitation).
- Patients and members of the public- lay summaries, press release, presentations at science festivals, infographics.

Co-applicant links with guideline organisations (Resuscitation Council UK, European Resuscitation Council, International Liaison Committee on Resuscitation) will support the implementation of research findings in clinical practice. As both interventions (IO and IV) are currently available to the NHS, we do not anticipate substantial barriers to implementation of the most effective strategy.

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