

PROTOCOL

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

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
CAG	Confidentiality Advisory Group (previously National Information Governance Board (NIGB)
CPC	Cerebral Performance Category
CRAG	Clinical Research Ambassador Group
CRF	Case Report Form
CPR	Cardiopulmonary Resuscitation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
EMS	Emergency Medical Services
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HSCIC	Health and Social Care Information Centre (HSCIC)
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit and Research Centre
ILCOR	International Liaison Committee for Resuscitation
IMP	Investigational Medicinal Product
IMPD	Investigation Medicinal Product Dossier
IQCODE	Informant Questionnaire Cognitive Decline Evaluation
JRCALC	Joint Royal College Ambulance Liaison Committee
LTFU	Lost to Follow Up
MHRA	Medicines and Healthcare Products Regulatory Agency
MMSE	Mini Mental Health State Examination
MREC	Main Research Ethics Committee
mRS	Modified Rankin Score
OHCA	Out of Hospital Cardiac Arrest
ONS	Office for National Statistics
PEA	Pulseless Electrical Activity
PSS	Personal Social Services
PTSD	Post traumatic stress disorder
R&D	Research and Development
RCT	Randomised Controlled Trial

Abbreviation	Explanation
ROSC	Return Of Spontaneous Circulation
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
UNTRAP	University/User Teaching and Research Action Partnership
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Over 50,000 people die each year following an out of hospital cardiac arrest (OHCA) in the UK(1, 2). Although initial resuscitation efforts restart the heart in about 25-30% of resuscitation attempts, most of these patients die in the next few days in hospital from severe brain damage(3) and overall survival (of attempted resuscitations) is less than 10%(1). Cardiac arrest causes a major burden on NHS resources (emergency treatment, post resuscitation care, rehabilitation) but treatment currently has a low chance of success.

The drug adrenaline has been an integral component of advanced life support from the birth of modern cardiopulmonary resuscitation in the early 1960s. In guidelines written originally in 1961, Peter Safar recommended the use of very large doses of adrenaline: 10 mg intravenously or 0.5 mg intracardiac(4). Animal studies show that injection of adrenaline during cardiac arrest increases aortic tone and thereby augments coronary blood flow(5, 6). However there are limited reliable data to assess the effects of adrenaline on long-term outcomes after cardiac arrest.

The International Liaison Committee for Resuscitation (ILCOR) synthesized the available evidence for adrenaline in 2010 (also re-assessed October 2012) and noted whilst it may improve the return of spontaneous circulation (ROSC) and short-term survival, there is insufficient evidence to suggest that adrenaline improves survival to discharge from hospital and neurological outcome. ILCOR stated that placebo-controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest are needed(7).

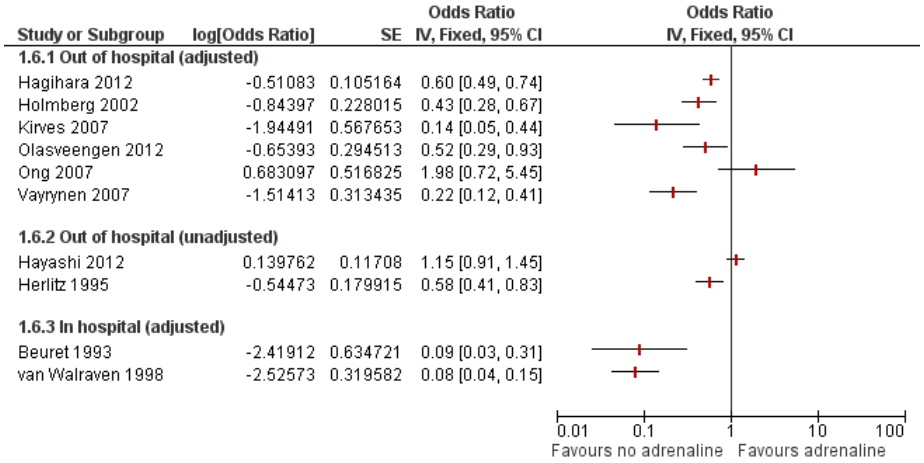
1.1.1 Summary of clinical evidence

A Cochrane review led by our collaborator (8)identified a single randomised, placebo controlled trial of intravenous adrenaline in OHCA (Search run Dec 2012). The PACA trial(9), conducted by our co-investigators Finn & Jacobs, was undertaken in Western Australia. The study aimed to enrol 5000 patients but at the time the study closed, only 601 patients had been randomised. The relatively small numbers led to the results having large uncertainty. The rate of ROSC [short term survival] was higher in those receiving adrenaline (64/272 (23.5%) vs. 22/262 (8.4%); OR 3.4, 95% CI 2.0 – 5.6), but there was not clear evidence of a benefit in survival to hospital discharge [long term survival]: adrenaline 11 (4.0%) vs. placebo 5 (1.9%) (OR 2.2, 95% CI 0.7 – 6.3). Two of the survivors in the adrenaline arm but none in the placebo arm had poor neurological outcome. In addition to the study's imprecision, interpretation of the findings is limited by a high level of post randomisation exclusions (n=67, 11%).

A second randomised study, conducted in Oslo, Norway compared intravenous (IV) cannulation and injection of drugs (including adrenaline) versus no IV cannula or drugs amongst 851 patients with OHCA(10). The patients in the IV group had better short-term survival (ROSC 165/418 (40%) vs. 107/433 (25%), OR 1.99, 95% CI 1.48-2.67)), however there was no clear difference in long term survival outcomes (survival to hospital discharge (IV arm 44/418 (10.5%) vs. no IV arm 40/433 (9.2%) OR 1.16 (95%CI 0.74-1.82); or favourable neurological outcome (Cerebral Performance Category [CPC] 1-2: IV 9.8% vs. no IV 8.1% OR 1.24 (0.77-1.98). The higher rate of ROSC was seen mainly in the patients with initial non-shockable rhythms (asystole and PEA): 29% vs. 11%. The rate of ROSC was 59% vs. 53% in those patients with an initial rhythm of VF/VT.

Observational studies enable large quantities of data to be collected but are often limited by selection bias, information bias and confounding. Statistical adjustment is often used to compensate for this, however unknown confounders may still lead to biased results. In a recent systematic review, we identified 16 observational studies comparing adrenaline use to no adrenaline use, including studies of adults and children in both in and out of hospital settings. Adrenaline fairly consistently improved short-term outcomes (4/5 studies reporting improved ROSC, OR range 0.86-2.24). The effect on long term outcomes was less certain (8/10 studies reported worse long term survival (OR range 0.09 – 1.98) and worse neurologically intact survival (3 of 3 studies, OR range 0.4 – 0.67) (11).

Figure 1 *Estimates of survival to hospital discharge or long-term survival from observational studies comparing adrenaline with no adrenaline*



In the post hoc analysis of the IV versus no IV trial, outcomes were examined according to whether the patient had actually received adrenaline(12). Treatment with adrenaline (n = 367) was associated with a greater chance of being admitted to hospital (OR 2.5; 95% CI 1.9 - 3.4). However long term survival outcomes were worse, with reduced survival to hospital discharge (adrenaline 24/367 (7%) vs. no adrenaline 60/481 (13%); OR 0.5; 95% CI 0.3 – 0.8) and reduced neurologically intact (CPC 1 or 2) survival (adrenaline 19/367 (5%) vs. no adrenaline 57/481 (11%); OR 0.4; 95% CI 0.2 - 0.7). These effects persisted after adjustment for confounding factors (VF, response interval, witnessed arrest, gender, age and tracheal intubation).

Three other recent studies in particular have suggested that adrenaline may cause worse long term outcomes. The largest observational study of adrenaline cardiac arrest involves 417,188 OHCAs in Japan(13). In propensity-matched patients, use of adrenaline was associated with increased rate of ROSC (adjusted OR 2.51; 95% CI 2.24 – 2.80) but a 1-month survival rate approximately half of that achieved in those not given adrenaline (adjusted OR 0.54; 95% CI 0.43 – 0.68). In another observational study from the Osaka group in Japan(14). 1013 (32.0%) of 3161 patients analysed received adrenaline. Those receiving adrenaline had a significantly lower rate of neurologically intact (CPC 1 or 2) one-month survival than those not receiving adrenaline (4.1% vs. 6.1% OR 0.69; 95% CI 95 % CI 0.48 - 0.98)).

An analysis of registry data has shown reduced survival in those who received adrenaline; The North American Resuscitation Outcomes Consortium (ROC) Epistry (n=16,000) found an inverse association between epinephrine dose and survival to discharge (survival >20% for those not requiring adrenaline, falling to < 5% for those requiring more than two doses. This finding persisted after

adjustment for age, gender, EMS witnessed arrest, bystander witnessed arrest, bystander CPR, shockable initial rhythm, time from 911 to EMS arrival, the duration of OHCA and study site(15). This was similar to a previous analysis of the Swedish Registry (n=10,000; odds ratio long term survival 0.43, CI 0.27-0.66)(16).

This creates the paradox of better short term survival at the cost of worse long term outcomes, in other words a "double edged sword"(17).

1.1.2 Mechanisms by which adrenaline may cause harm

There are a number of mechanisms through which adrenaline may cause harm. These can be considered under the following headings:

1.1.2.1 Reduced micro-vascular blood flow and exacerbation of cerebral injury

In animal models of cardiac arrest, adrenaline increases coronary perfusion pressure (which predicts restarting the heart) but impairs macro and micro-vascular cerebral blood flow. Specifically adrenaline is noted to reduce carotid blood flow(18), micro-vascular blood flow(19), causing worsening cerebral ischaemia(20).

1.1.2.2 Cardiovascular toxicity

In a further analysis of the Norwegian IV versus no IV trial(10), adrenaline increased the frequency of transitions from PEA to ROSC and extended the time window for ROSC but at a cost of greater cardiovascular instability after ROSC, with a higher rate of re-arresting. These observations are consistent with other studies which link adrenaline with ventricular arrhythmias and increased post-ROSC myocardial dysfunction (21). In human studies with patients with sepsis (22) or acute lung injury (23), β agonist stimulation is similarly linked to cardiovascular instability and reduced survival (24). A systematic review of β blocker treatment in animal models of cardiac arrest found fewer shocks were required for defibrillation, myocardial oxygen demand was reduced and post resuscitation myocardial stability improved with less arrhythmia and improved survival(25).

1.1.2.3 Metabolic effects

Adrenaline causes lactic acidosis(26) which is associated with poor outcomes after cardiac arrest(27, 28). It also induces stress hyperglycaemia which is also associated with poorer outcomes (29).

1.1.2.4 Immunomodulation and predisposition to infection

Infective complications, including bactaremia and early onset pneumonia are common after OHCA and associated with worse outcomes(30). The immune-modulatory effects of beta agonists have been well characterised and may reduce host defence to infection(31) which may contribute to an increased susceptibility to post resuscitation sepsis.

1.1.3 Summary of effects

Use of adrenaline in cardiac arrest increases short-term survival [ROSC] but there remains doubt whether this is translated into increased long-term outcomes. Observational studies suggest an association between adrenaline and worse long-term survival.

1.2 Research Question

Is the use of adrenaline in out of hospital cardiac arrest clinically and cost effective?

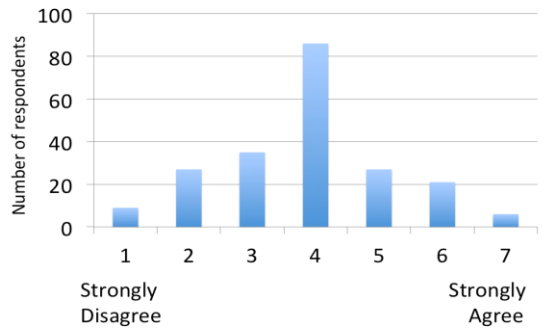
1.3 Need for a trial

Whether the practice of giving adrenaline is effective or not therefore remains an important question that needs to be answered. Uncertainty about adrenaline has been raised by recent evidence suggesting that it may be harmful. Resolution of this uncertainty is urgent, as adrenaline is used widely to treat cardiac arrests, and if harmful, may be responsible for many avoidable deaths. There are several precedents where treatments have been evaluated after years or decades of use and have been found to be ineffective or harmful, including pulmonary artery catheters in intensive care(32), beta agonists for acute respiratory distress syndrome (ARDS)(23) and corticosteroids for head injury(32). It is possible that adrenaline for cardiac arrest may be a similar case.

The International Liaison Committee on Resuscitation appraised the evidence surrounding adrenaline in OHCA in 2010(7) and again in Oct 2012 (Vienna, 2012). They concluded there is an urgent need for randomised, placebo controlled trials of adrenaline.

To assess attitudes of the UK clinical community we conducted a written survey of 213 attendees (doctors, nurses, paramedics) at the Resuscitation Council (UK) Annual Scientific Symposium in September 2012 to assess the scientific and clinical communities' current perspectives on the role of adrenaline for the treatment of cardiac arrest. Respondents expressed their agreement to a series of statements on a 7 point Likert scale (1 = strongly disagree, 7 strongly agree). Respondents reported that adrenaline increased short term survival (median score 6 (IQR 6-7), but disagreed that it improved long term outcomes (median score 2 (IQR 2-3)). There was greatest uncertainty about the balance of risks and benefits of IV adrenaline (figure 2a). Respondents felt the most pressing future research need for the NHS was a trial comparing adrenaline to placebo (figure 2b).

Figure 2



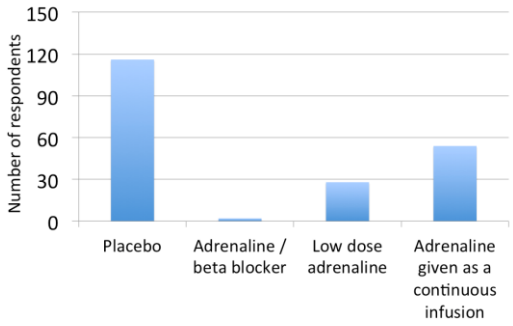


Figure 2(a): Overall, the risks of IV adrenaline in cardiac arrest outweigh the benefit

Figure 2(b): In a trial, the standard dose of adrenaline should be compared with which of the following?

A trial addressing this question is timely, because of the recent publication of studies questioning the effectiveness of adrenaline, and calls for a large scale randomised controlled trials (RCT) to resolve this issue. There are no other completed, on-going or planned trials in the clinicaltrials.gov or controlled-trials.com databases. Moreover, recent research projects (e.g. PARAMEDIC trial(33)) have shown the feasibility of conducting large scale OHCA trials in the UK. The learning from this trial, undertaken by this group, will help to ensure efficient and successful recruitment.

The emerging data suggest a number of experimental strategies could be considered including comparing adrenaline to alpha 2 agonists, adrenaline with beta blockade, lower dose adrenaline or adrenaline as a continuous infusion. The timing of adrenaline administration may also be important, however this is primarily dependent on ambulance response times which would be difficult to control for in a randomised trial. We suggest the most pressing need is for a definitive trial comparing standard dose adrenaline (1mg every 3-5 minutes) to placebo. Until there is clarity about the effect of adrenaline on long-term outcomes the best comparator agent (placebo or standard dose adrenaline) for trials of other agents remains unknown.

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

1.4 Good Clinical Practice

The trial will be carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practise (GCP), and applicable UK legislation, as well as WCTU Standard Operating Procedures (SOPs).

In the context of these guidelines adrenaline is considered the investigational medicinal product under investigation (the intervention).

2. TRIAL DESIGN

2.1 Trial summary

This is a pragmatic, individually randomised, double blind, controlled trial and economic evaluation.

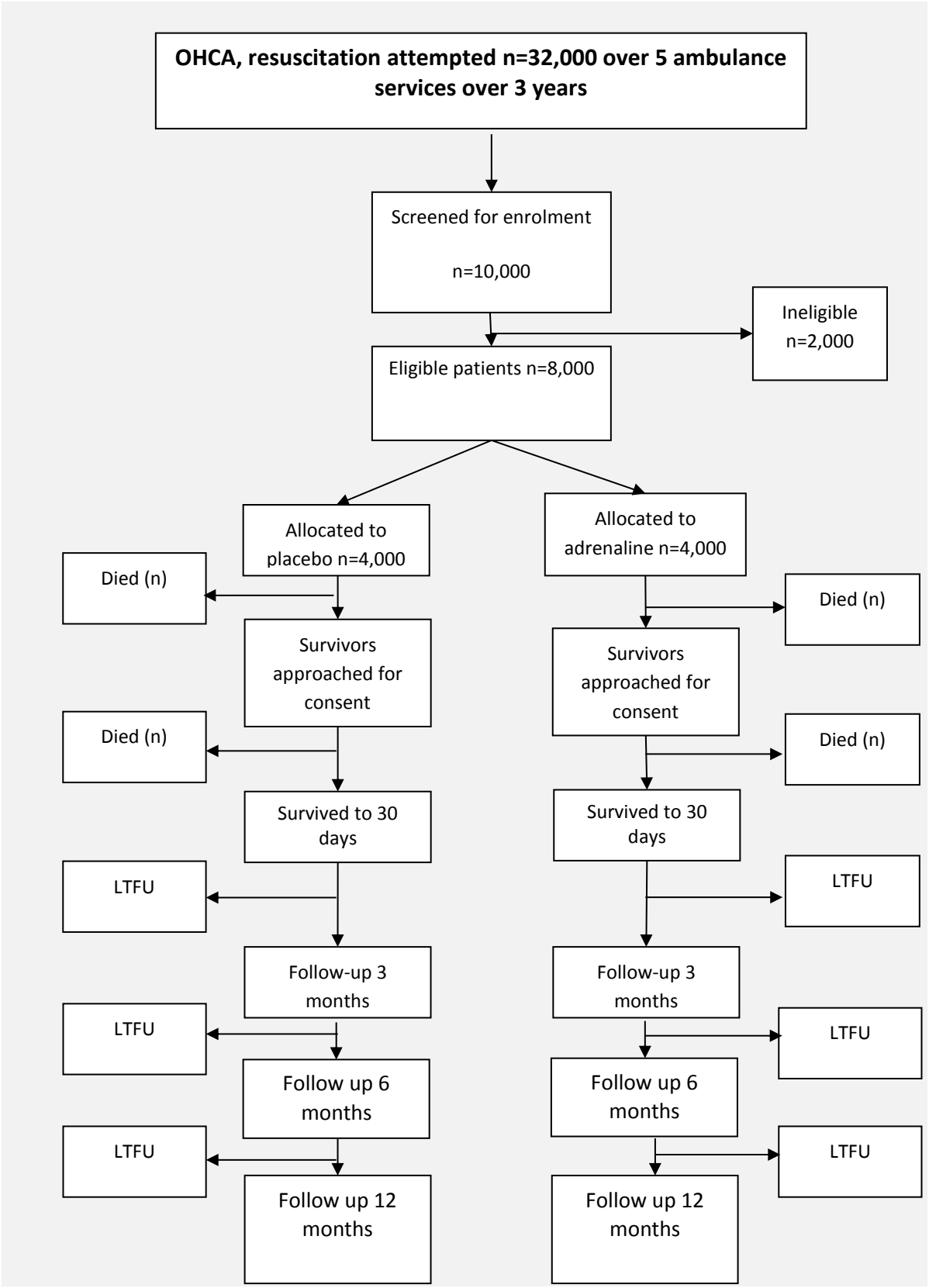
Patients will be eligible if they are in cardiac arrest in the out-of-hospital environment and advanced life support is initiated. Exclusions are cardiac arrest as a result of anaphylaxis or life threatening asthma, patient known or appears to be under 16 and known or apparent pregnancy.

Patients will be randomised to either adrenaline (intervention) or placebo (control). Randomisation will occur when the trial IMP pack has been opened.

Outcomes are survival to 30 days (primary outcome), survival to hospital discharge, 3, 6 and 12 months, health related quality of life, health economics, neurological and cognitive outcomes (secondary outcomes).

All survivors will be contacted and invited to take part in the follow up (at 3 and 6 months).

Figure 3. Flow chart for PARAMEDIC-2 trial



2.1.1 Pilot Study

There will be an internal pilot to test that the components of this trial work together. The internal pilot will run for 6 months (from months 7-12). The data from the internal pilot will be included in the main trial. During the pilot we will measure recruitment rate, compliance with allocated intervention and that the approach to data collection and follow-up works effectively. It is intended to run seamlessly into the main trial.

The results of the pilot study will be reviewed with the TSC, DMC and representatives from the HTA specifically considering the achievement of the following targets:

- 25% of ambulance staff trained (i.e. majority (80%) participating staff at 25% of stations)
- 181 patients recruited within 6 months of first randomisation
- Data available on primary outcome >98%
- Proportion of patients who are alive agreeing to follow–up >75%
- Reconcile IMP packs with patients enrolled in the trial
- Review of our approach to inform patients and relatives of trial participation
- Review of feasibility to collect secondary outcomes

2.2 Objectives

2.2.1 Primary objective

The primary objective of this trial is to determine the clinical effectiveness of adrenaline in the treatment of OHCA measured as primary outcome: 30 day survival**.**

2.2.2 Secondary objective

Secondary objectives of the trial are to evaluate the effects of adrenaline on survival, cognitive and neurological outcomes of survivors and to establish the cost-effectiveness of using adrenaline.

2.3 Outcome Measures

2.3.1 Efficacy

Primary outcome:

Survival to 30 days post cardiac arrest.

Secondary outcomes:

1. Survived event *(sustained ROSC, with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital)*
2. Survival to hospital discharge *(the point at which the patient is discharged from the hospital acute care unit regardless of neurological status, outcome or destination)* 3, 6 and 12 months
3. Neurological outcome (modified Rankin Scale (mRS)) at hospital discharge, 3 and 6 months
4. Neurological outcomes (IQCODE and "Two simple questions") at 3 and 6 months
5. Health related quality of life at 3 and 6 months (SF12 and EQ-5D)
6. Cognitive outcome at 3 months (Mini Mental State Examination (MMSE))

7. Anxiety and depression at 3 months (Hospital Anxiety and Depression Scale (HADS))
8. Post Traumatic Stress at 3 months (PTSD civilian checklist (PCL-C))
9. Hospital length of stay
10. Intensive care length of stay

The outcomes defined by the Utstein convention for reporting outcomes from cardiac arrest (34) will be reported.

mRS will be measured at hospital discharge, 3 and 6 months. mRS was selected over Cerebral Performance Category (CPC) as it is more sensitive to detect mild cognitive impairment. It can be reliably extracted from medical records and is a predictor of long term survival. There is emerging international consensus (Utstein 2012/2013) that mRS should be the primary measure of neurological outcome in cardiac arrest trials. mRS is a 7 point scale ranging from mRS 0 (no symptoms) to 6 (dead). The spectrum of impairment of health related quality of life following cardiac arrest includes memory and cognitive dysfunction, affective disorders PTSD(35). The number of patients expected to survive to hospital discharge is anticipated to be in the region of 400-600, which will allow more intensive follow-up. The SF-12 is a standard quality of life measure that is short and easy to complete. In additional the EQ-5D will be used as a health utility measure for the health economic analysis.
Cognitive function will be assessed using the MMSE(36). The informant questionnaire cognitive decline evaluation (IQCODE) and the "Two Simple Questions" tool will form supplementary assessments of cognitive function. The PTSD Civilian Checklist (PCL-C)(37) is a 17-item self-administered questionnaire measuring the risk of developing PTSD and has been used in previous studies as a good surrogate for the clinical diagnosis of PTSD, which would require a face to face interview by a suitably trained professional. The HADS is a 14-item self administered questionnaire which has been previously used successfully to measure affective disorders in cardiac arrest survivors(38). Two of these measures (PCL-C and HADS) are being used as part of a multi-centre follow-up for people surviving a critical illness (Intensive Care Outcome Network (ICON) study), which can be used as a reference population(39).

2.3.2 Safety

There will be a system for reporting adverse events and serious adverse events in addition to the trial outcomes by participating ambulance clinicians (see Section 4).

See section 6.2 for information relating to interim analyses and early stopping criteria.

2.3.3 Health Economics

Primary Economic Outcome:

Incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS and personal social services (PSS).

Secondary Economic Outcomes:

Cost of critical care stay (level 2/3 days); cost of hospital stay; utilisation of NHS and PSS resources after discharge; broader resource utilisation after discharge.

2.4 Sample Size

2.4.1 Incidence of primary outcome

Most existing data refer to survival to hospital discharge rather than survival to 30 days, but as most mortality will occur in the first days after cardiac arrest, we expect these two measures to be very similar. Estimates of long-term survival of patients who receive adrenaline during a resuscitation attempt vary between about 3.5% and 12%. From national data for England, overall survival to hospital discharge of patients for whom resuscitation is attempted is 7%(1). However, this will include a small number of patients who achieve ROSC immediately and would not receive adrenaline, hence would not be recruited to the trial. As these patients have much better outcomes, the survival among the trial population will be slightly lower. Estimates from the Norwegian trial of intravenous drugs and the Australian trial of adrenaline were 9%(10) and 4%(9) respectively. In the PARAMEDIC trial, survival for patients who received adrenaline is 6%, and in the REVIVE airways study, where most patients will have received adrenaline, it is 8.5% (personal communication J Nolan). We therefore expect survival to 30 days of approximately 6% in the adrenaline group.

The trial's primary aim is to estimate the treatment effect of adrenaline and the uncertainty around this; we have therefore based the target sample size primarily on the precision of the estimate of the risk ratio(40). Figure 4 shows the precision that is achievable (width of the 95% confidence interval for the risk ratio) with different total sample sizes, for risk ratios (placebo versus adrenaline) of 1.25 and 1.00. A risk ratio of 1.25 corresponds to an increase in 30-day survival from 6% in the adrenaline group to 7.5% in the placebo group.

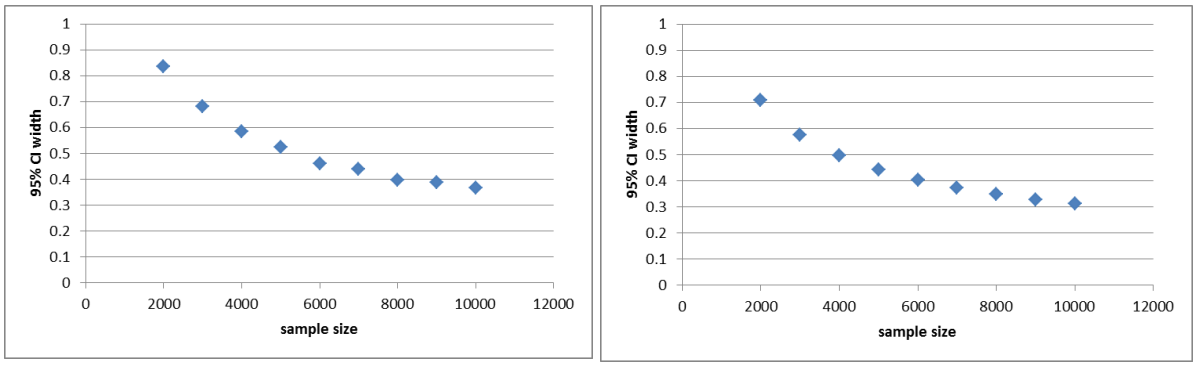


Fig. 4. Width of 95% confidence interval for the risk ratio against sample size, for RR 1.25 (left) and RR 1.0 (right), with 6% survival in the adrenaline arm.

2.4.2 Sample size

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

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

2.5 Eligibility Criteria

2.5.1 Inclusion Criteria:

Patients will be eligible if both the criteria below are met:

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

2.5.2 Exclusion criteria at the time of arrest will be:

1. Known or apparent pregnancy
2. Known or apparently aged under 16 years
3. Cardiac arrest caused by anaphylaxis or life threatening asthma
4. Adrenaline given prior to arrival of ambulance service clinician

2.6 Ethical and legal considerations

Conducting research in emergency situations where a patient lacks capacity is regulated by The Medicines for Human Use Act (UK Clinical Trial Regulations) and amendment 2006 which relates to Article 5 from the EU Directive 2001 and National Research Ethics Committee Informed Consent Guidance (version 3 1 May 2008).

We have based our assessment of the ethical considerations for this trial on the template outlined at the Health Research Authority Workshop 2012 on conducting emergency research in patients who lack capacity.

2.6.1 What happens to someone when they sustain a cardiac arrest?

A cardiac arrest is the medical term used to describe sudden cessation of the heartbeat. Outside of a hospital cardiac arrest is usually a sudden, unexpected event. When cardiac arrest occurs blood stops circulating around the body and consciousness and mental capacity are lost within seconds. Treatment must be started urgently – every second that treatment is delayed is associated with less chance of survival. Treatment comprises combinations of CPR (chest compressions and ventilation), electric shocks and other advanced treatments. Treatment is usually continued for up to 20 minutes. After this time window the chances of survival are very small. If the heart is re-started the person is taken to hospital. Most people that survive initially are unconscious when they arrive in hospital and are admitted to intensive care. Unfortunately many people die within the first 24 hours of admission to hospital. People surviving more than 24 hours are treated in intensive care for around 4-6 days. Most remain unconscious for the majority of the time in intensive care. People that recover (about 1 in 20 of those initially treated by the ambulance service) are discharged to the hospital ward. Most people will have regained capacity by this point but some will have sustained brain damage and may never regain capacity.

Footnote: Cardiac arrest is different from the term heart attack. A heart attack refers to the blockage of one of the blood vessels supplying the heart with blood. Although some heart attacks may progress to cardiac arrest – most do not. Most people survive a heart attack, whilst few survive a cardiac arrest.

2.6.2 Is this research needed and is there uncertainty about treatment?

The Resuscitation Council (UK), Association of Ambulance Medical Directors and ILCOR have identified the need to conduct a placebo controlled trial of adrenaline use in cardiac arrest.

Section 1 of the protocol summarises the current evidence about the use of adrenaline as a treatment for cardiac arrest. In brief there is some evidence that adrenaline leads to better short-term survival. Whether it improves long-term survival and how it affects brain function after cardiac arrest is uncertain. Whilst some studies suggest it may be beneficial, others suggest it may be ineffective or potentially harmful. Our survey of UK clinician's views about the effectiveness of adrenaline shows substantial uncertainty amongst the clinical community (see protocol figure 2a).

2.6.3 Is there a need to recruit participants who lack capacity?

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

2.6.4 In the context of the research is consent or consultation feasible?

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

2.6.5 Does treatment need to be given quickly and might delay change the effect of treatment or the results?

Treatment (in the form of CPR) must be started immediately in an attempt to save the person's life. Delay in the initiation of CPR and other emergency treatment (e.g. defibrillation) is associated with worse outcomes. Observational studies suggest that if adrenaline is effective, the earlier it is given the more likely it will be beneficial (41) (42, 43).

2.6.6 Will procedures accommodate variations in capacity?

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

2.6.7 Is it practical to consult a professional legal representative unconnected to the research?

In this setting it will not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying emergency treatment.
We consider it unlikely that even if it were possible to seek consent from a personal legal representative, that in light of the emotional distress of the cardiac arrest will cause, that any such person would be likely to have the capacity to make an informed decision in the limited time available.

2.6.8 What should the patient or legal representative be asked later?

We will seek consent to continue in the trial. Our rationale is that the patient will be enrolled in the trial at the time of their cardiac arrest if they meet the eligibility criteria. The duration of the research intervention (adrenaline or placebo) will typically last for 5-20 minutes and rarely more than 45 minutes. Adrenaline is rapidly metabolised by the body after administration with a half-life duration of 5-10 minutes (time it takes for the body to remove half the drug). The intervention phase of the trial will therefore be complete within an hour of the patient sustaining a cardiac arrest.
We will approach patients or their legal representative, as soon as practicable after the initial emergency has passed to inform them of their participation and request consent to continue using the steps outlined below.

2.6.9 Provision of general information about the trial

We will ensure that general information about the trial and contact details for further information is freely available throughout the trial. This will be achieved through including information about the trial on Ambulance Trust and University websites, Ambulance Service Public Newsletters, Posters / information leaflets, discussion at public meetings, Annual reports etc.

We have developed a system to allow a patient to decline participation in the trial in the event that they sustain a cardiac arrest. Requests not to participate will be sent to and managed by the WCTU Trial Team. An online form can be completed on the website or the team can be contacted by phone or email. A stainless steel “No Study” bracelet will be issued to the person’s home address and with the person’s permission their home address will be passed to the ambulance service to register the person’s wishes. They will also be told to tell those close to them their wishes and that those wishes will be respected by the treating paramedics. Paramedics are trained to look for the bracelet.

2.6.10 Informing the patient about participation in the trial:

The first attempt to contact the patient and inform them of their enrolment into the trial will be during their stay in hospital before hospital discharge. We plan to make contact as soon as practically possible after the initial emergency has passed and taking the utmost care and sensitivity in doing so. Following our experience from a 4,400 patient study in out of hospital cardiac arrest (PARAMEDIC trial) and talking to fellow researchers from the REVIVE(44)cardiac arrest study and discussions with patient and public representatives, we believe the earliest practicable time to contact patients and relatives is once the patient is discharged from ICU and is on a hospital ward. This allows sufficient time for the research team to be made aware of enrolment, identify who the patient is, check which hospital the patient was transferred to, whether they are still alive and to verify with the hospital team where the patient is within the hospital. Transfer to a ward will indicate that the initial emergency has passed and the patient’s condition will have stabilised. It is also more likely that the patient has regained consciousness and it will avoid any confusion or additional distress of making an approach while the patient remains critically ill in intensive care.

Procedure

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

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

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

2.6.11 Participants who lack capacity

In the event that a patient lacks capacity to consent, the Research Paramedic will work with the hospital team to identify a legal representative as defined below:

Personal Legal Representative:

- A person independent of the trial, who by virtue of their relationship with the potential study participant is suitable to act as their legal representative for the purposes of that trial, and who is available and willing to so act for those purposes.

Or if there is no such person:

Professional Legal Representative:

- A person independent of the trial, who is the doctor primarily responsible for the medical treatment provided to that adult.
- Or a person nominated by the relevant healthcare provider

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

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

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

2.6.12 Contact Patient at Home Address:

If a patient is discharged from hospital before contact can be established an invitation letter and information sheet will be posted to their discharge address as soon as possible.

If there is no response after 2 weeks the WCTU team will try and contact the patient by phone (if phone number is known) or by a second letter. If the patient wishes to be contacted about the trial they can contact the WCTU by phone, or by email, or by returning the reply slip.

For a small number of patients, if there is a delay between discharge and contacting the patient, to be sure the patient is still alive before writing, the ambulance service will conduct its own checks on patients' survival using its own data systems, which will differ between services. Where possible, they will consult the NHS Patient Demographics Service, but access may not have been set up in all areas.

Other checks carried out by either the ambulance service and or the WCTU trial team may include contacts with GPs (where known), hospitals or Health and Social Care Information Service (HSCIC).

To ensure we write to the correct address, we will confirm the patient address with hospitals, GPs or public access online systems such as 192 before writing.

After these checks, if someone is still believed to be alive the WCTU will contact them at their home address by letter, as detailed above.

2.6.13 Postal Questionnaires and capacity

Specific guidelines have been written by the trial team if the scenario arises that a legal representative responds on behalf of the patient to an invitation letter by post and indicates they want to take part with postal questionnaires only (i.e. capacity cannot be established face to face).

2.6.14 Obtaining Consent

The research team, or hospital staff where specific R&D approval has been obtained, will be fully trained on informed consent and assessing capacity, GCP guidelines, relevant legislation and the trial related procedures around consent.

Informed consent will ideally be taken with the patient or their legal representative on the hospital ward. In exceptional circumstances if consent was not obtained during the hospital stay, the patient responds to the invitation letter sent by post and agrees to have a home visit, written consent would be taken at the 3 month visit.

The consent form will list the different sorts of information that we wish to collect. We will not seek specific consent to use the data already collected. If the patient or legal representative does not want the trial team to continue to collect data about the patient's survival, or to access the patient's health records then they can indicate this on the consent form by not initialling the corresponding boxes or by telling the trial team verbally.

Staff will confirm the patient's willingness to continue with the trial at each contact point.

2.6.15 People that do not survive:

Key issues:

The sad reality of an out of hospital cardiac arrest is that less than 1 in 10 survive. Suffering the sudden unexpected loss of a loved one due to cardiac arrest is a traumatic event that frequently leads to symptoms of anxiety, depression and post-traumatic distress (45, 46). Careful consideration therefore needs to be given to how, when and if the relatives of non-survivors are informed about participation in the trial.

By the time the patient's death has occurred the trial intervention will have been implemented and no further follow up will occur. Thus there is no requirement to or utility in seeking consent to continue. The purpose of any communication with the family/next of kin of the deceased is therefore to inform them about the patient's involvement in the trial. Informing the family about the trial ensures that the process of trial recruitment is open and transparent. It reduces the likelihood that family members will discover at a later date that their relative was involved in a trial without their knowledge. However, knowledge of the trial participation after the event may also place a significant burden on the next of kin at a time of heightened emotional distress due to the loss of their relative or friend. Any strategy to inform family or next of kin following a patient's death needs to carefully balance the need for transparency with the need to minimise their distress.

Strategies for informing relatives

There are a number of ways in which we could approach informing the relatives of those that do not survive. These can be broadly categorised as passive or active methods. Passive methods include placing information about the trial in publically accessible places (e.g. websites, newsletters) and targeted sites 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. An advantage of passive methods is that they allow people to make a choice about whether they wish to seek further information and the timing of that approach. The disadvantage of passive methods is that one cannot be certain that relatives of all participants will see them. Discussion with investigators of previous UK trials (e.g. CRASH trials, Brain injury trials) indicates that passive strategies, although not formally evaluated, have been used successfully.

Active strategies involve making direct contact with relatives (e.g. posting or hand-delivering a participant information leaflet, organising for a face to face meeting or telephone call). Concerns about the potential burdens to inform recipients and the practicalities of this approach mean that it has not been used in previous UK out of hospital cardiac arrest trials (e.g. LINC [mechanical CPR], PARAMEDIC-1 [mechanical CPR], REVIVE [airway device]) [personal communication with Chief Investigators]. We are therefore unable to draw on relatives or researchers experience of this process.

There are practical barriers to providing information actively. The sudden and unpredicted nature of cardiac arrest mean that the relatives / next of kin are neither universally present nor identifiable at the time of the cardiac arrest. Information on the identity of the relatives / next of kin are also not held by ambulance services.

For people where resuscitation efforts are terminated in the home (approximately 40% of total cases) it is not possible for the paramedic who attends the cardiac arrest to spend the necessary

time to explain about the study and answer questions due to the high likelihood that they will be tasked to attend another life threatening incident before the informing process is complete. This approach would also require that every paramedic was trained to discuss the trial with the family in this setting.

For patients that die early in hospital (before consent is obtained), there is likely to be a delay in notification to the ambulance service making an in-hospital visit impractical.

Given these difficulties with face-to-face consultation an alternative is to send written information by post. Outwith the difficulties described above about the accuracy and completeness of contact details, we have concerns that this un-solicited approach and absence of an opportunity to ask questions immediately upon receipt could exacerbate an already traumatic and stressful experience.

Advantages of active approaches are that the process of information giving can be more actively monitored. Whether it leads to greater dissemination of information, given the practical difficulties described is unclear. Disadvantages are active approaches remove the relatives choice about whether they wish to receive information about the trial or be reminded about the final stages of the deceased life and the risk that the receipt of such information causes additional distress.

We have carefully considered the benefits and burdens of different approaches to informing the relatives of the deceased, to inform them about the trial.

Our assessment of the balance of benefits and burdens for relatives is that the burden of actively informing them will outweigh the potential benefit. We propose therefore to inform relatives through passive communication processes described above. We will monitor how this approach works during the pilot phase of the study and if necessary revise during the progression to the main trial. We have discussed this in detail with our clinical ethicist and patient representatives and have their support for this approach.

2.6.15.1 Enquiries regarding trial participation:

If a member of the public would like to enquire whether their next of kin was enrolled into the PARAMEDIC2 Trial they will be able to complete a Trial Participation Enquiry Form. On receipt of a completed Trial Participation Enquiry Form the PARAMEDIC2 Trial Office will work with the appropriate site to check whether the next of kin of the enquirer was enrolled into the PARAMEDIC2 Trial. Once it is confirmed a letter will be sent from the appropriate ambulance service to confirm whether the enquirer's next of kin was enrolled into the trial along with an information sheet about the trial, which will include contact details for the PARAMEDIC2 Trial Office.

2.7 Randomisation

Patients will be enrolled by the attending ambulance service clinicians, who will determine whether a resuscitation attempt is appropriate (according to Joint Royal College Ambulance Liaison Committee (JRCALC) guidelines), and if so, whether the patient is eligible. If the patient meets the eligibility criteria, he or she will be randomised into the trial. Because recruitment takes place in an emergency situation, telephone or internet randomisation is impractical, and the trial will therefore use a system of pre-randomised treatment packs. Trial IMP will be packaged in numbered treatment packs. The pre-randomised sequence will be prepared by the trial statistician. All packs will be identical in appearance; hence clinicians, patients and trial personnel will be unaware of whether any specific

pack contains adrenaline or placebo. Treatment packs will be supplied to each ambulance service, in a central location and will be distributed from there to participating ambulance stations and vehicles. When ambulance service personnel identify an eligible patient, randomisation will be achieved by opening one of the packs carried by the vehicle attending the arrest.

Vehicles will also carry their standard supply of adrenaline, for use only with ineligible patients.

It is likely that in some cases, a trial IMP pack will be opened before a patient becomes eligible. This may occur when for example, a patient is found to have a shockable rhythm; the IMP pack may then be opened in anticipation of eligibility, so that the trial IMP can be given immediately if the patient does not respond to defibrillation. A proportion of such patients will, however, achieve ROSC, and hence not become eligible for the trial, and the trial IMP would therefore not be administered. Opening of the IMP pack (i.e. randomisation) will be recorded for such patients, and their number will be reported in the trial flowchart, but they will not be counted as part of the trial recruitment, no further data will be collected and they will be excluded from the analysis of outcomes.

We have decided to use the moment of opening the trial IMP pack rather than the moment of IMP administration as the time of randomisation, because the latter would exclude genuinely eligible patients for whom a IMP pack is opened but the IMP is not administered. This is expected to be rare, but any such patients should be included in a pragmatic trial.

2.8 Post-Randomisation Withdrawals and Exclusions

Patients who receive trial IMP but are later found to be ineligible will be included in the analysis and will be followed up to 12 months.

Patients who decline to be contacted will be logged on the database from the point that they communicate their intention to the trial team and no further contact will be made. Data already collected will be retained and included in the analysis unless otherwise indicated.

The information sheet explains the trial and the data that will be collected. The consent form splits out the different data that could be collected about them, and gives the patient the option to decline. NHS records will continue to be used unless the patient explicitly declines permission for this, as will tracking of the patients via HSCIC to determine survival to 12 months post cardiac arrest.

In the rare situation where a patient has neither consented, nor declined follow-up they will not be included in the face to face follow-up, but data collection from NHS records and HSCIC will continue.

2.9 Blinding

2.9.1 Methods for ensuring blinding

The packaging and the labelling of the IMP packs will not give away which IMP is being used therefore the patient, attending clinicians, Research Paramedics and trial administration team will be blinded. Only the statistician will be able to link the IMP pack number to the allocation of adrenaline or placebo.

2.9.2 Methods for unblinding the trial

The Chief Investigator retains the right to break the code for serious adverse events that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. The CI will unblind if requested to do so by a Coroner as part of a death enquiry. In exceptional circumstances, the CI will also consider requests for unblinding from patients or, if they lack capacity, family members/next of kin. This can only occur if the request is made after the benefits and harms of disclosing this information to them have been discussed.

Otherwise treatment codes (IMP pack number) will only be broken for the planned interim analyses of data by the statistician at the request of the Data Monitoring Committee (DMC).

2.9.3 Methods for unblinding the trial – after trial completion

Requests for unblinding of treatment allocation may be received (either from survivors or from the next of kin of trial participants that have deceased) after completion of the trial. Where these requests are received the PARAMEDIC2 Trial Office will send the enquirer (on behalf of the Ambulance Services) an information sheet about unblinding and a response form for completion if they wish to continue with unblinding after having read the information provided. Once a completed response form is received, requesting unblinding, the PARAMEDIC2 Trial Office will respond to confirm the treatment allocation (once appropriate checks have been performed) on behalf of the Ambulance Services with Ambulance Service contact details for further queries.

2.10 Trial Intervention / Treatments

Participants will receive resuscitation according to the Resuscitation Council (UK) and JRCALC Advanced Life Support Guidelines. All standard advanced life support interventions will be provided including chest compression, defibrillation and advanced airway management as required with the exception that standard adrenaline will be substituted with trial IMP drawn from a single trial treatment pack.

Trial treatment packs will be arranged by MODEPHARMA and will be labelled according to EudraLex Volume 4 Annex 13 requirements. They will contain active IMP (adrenaline) or matching placebo.

2.10.1 Adrenaline Arm (intervention)

Adrenaline 1mg will be supplied in pre-filled syringes within numbered trial treatment packs. They will be identical in appearance to placebo.

2.10.2 Placebo Arm (control)

Placebo will be supplied in pre-filled syringes within numbered trial treatment packs. They will be identical in appearance to adrenaline.

2.10.3 IMP Storage, Dispensing and Destruction

A shelf-life of minimum 6 months will be assigned to the trial packs (subject to MHRA approval). A 24 month ICH stability study will be run in parallel and a shelf-life extension program can be considered.

IMP packs will be stored in the storage room at ambulance stations as well as on vehicles as per normal practice.

The number of IMP packs "dispensed" on each vehicle may vary between ambulance services and within ambulance services and will be detailed in the trial operations manual.

Any syringes not used within the trial IMP pack will be destroyed as per local ambulance service operations and documented.

2.10.4 IMP Accountability and Monitoring

All uses of trial IMP packs will be documented on accountability logs. The trial will utilise the ambulance services systems for documenting receipt, dispensing, returns and destruction of IMP packs.

The attending clinician will be required to document on the patient record the IMP pack number how many syringes were used from the IMP pack.

Trial IMP will be reconciled where possible on station and also with the trial database which detail patients who have been enrolled and the trial IMP packs that were used.

2.10.5 Training

A programme of training will be provided to ambulance personnel and air ambulance staff (where relevant) participating in the trial. This will include the following:

- Trial background
- Randomisation procedures
- Basic GCP principles
- Inclusion and exclusion criteria
- Data collection and documentation
- Ethical issues and consent

In addition all training information and training materials will be made available via the trial website. Each Trust will record and maintain training logs and report a summary to the WCTU.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 1

	Day 0 Cardiac Arrest	**Hospital**	**Day 30**	**Week 6** *Letter to Patient (if missed in hospital)*	**Month 3 (2-4)** Follow up visit	**Month 6 (5-10*)** Postal	**Month 12 (12)**
Inclusion/ Exclusion Criteria	✓	x	x	x	x	x	x
Cardiac Arrest Data	✓	x	x	x	x	x	x
Patient Identifiers *(if applicable)*	✓	✓	x	x	x	x	x
Adverse Event Reporting	✓	✓	x	x	x	x	x
Survival Checks	✓	✓	x	✓	x	x	✓
Survival Status	✓	✓	✓	x	✓	✓	✓
Quality of CPR	✓	x	x	x	x	x	x
Hospital stay data (LoS)	x	✓	x	x	x	x	x
Neurological Outcome mRS	x	✓	x	x	✓	✓	x
Notification of enrolment and invitation to take part in the follow up	x	✓	x	✓	x	x	x
Informed Consent	x	✓	x	x	✓	x	x
Neurological outcomes: IQCODE and 2 simple questions	x	x	x	x	✓	✓	x
Health Economics Questionnaire	x	x	x	x	✓	✓	x
Quality of Life Questionnaires: SF-12 and EQ-5D	x	x	x	x	✓	✓	x
Functional outcomes: MMSE, HADS, PTSD	x	x	x	x	✓	x	x

**The 6 month data collection window can be longer in the early part of the trial but for patients enrolled in month 36, data will need to be retrieved at 6 months.*

3.2 Data collection

3.2.1 Patient Enrolment

All cardiac arrests where a trial pack is opened will be reported to the WCTU promptly. Mechanisms for providing this information will be specific to each ambulance service.

3.2.2 Hospital

Patients may be taken to any hospital in the trial regions. Although hospital clinicians will not have a role in delivering the trial interventions, they will be informed about the trial and will be provided with information about the trial for any clinicians or patients that need it.

Hospitals will be contacted initially to ascertain survival of patients handed over from ambulance services to the ED. If the patient has survived, the research paramedics will liaise with the hospital clinicians to visit the patient and seek consent for continuation in the study (see Section 2.6.10).

For any patient taken to hospital we will seek data on survival, length of stay in hospital and on ICU, targeted temperature management, adrenaline use and mRS score at discharge as well as discharge address and GP details. As some patients are found in a public place without any identifiers or only part of their details are known to the ambulance service at the time of arrest, hospitals will also, where necessary, provide missing information such as name, address, date of birth.

3.2.3 Follow-up

Survivors willing to take part will be followed up approximately 3 months and 6 months after their cardiac arrest as per table 1. Wherever possible the 3 month assessment will be by home visit, but if the patient prefers postal questionnaires or to go through the questionnaires over the telephone this can be arranged although MMSE cannot be done over the phone. Data for the 6 month follow up will be issued from WCTU and returned by post.

Following the approach to the patient, in the unlikely event that we have not obtained a response from the patient after 1 month, we will approach the patient's GP or hospital or ambulance service for information on their mRS score as close to 3 and 6 month time points as possible.

Where we have not been able to collect data about the patient's stay in hospital such as length of stay on ICU, this will be collected from electronic data sets such as Intensive Care National Audit and Research Centre (ICNARC), National Institute for Cardiovascular Outcomes Research (NICOR), Patient Episode Database for Wales (PEDW) and or Hospital Episode Statistics (HES). These data sets will also be used for the health economic analysis.

3.2.4 Quality of CPR

Information on CPR quality is increasingly being collected by NHS Ambulance Services.

Trial sites that collect these data as part of standard practice will share CPR quality measurements for patients enrolled in the trial with WCTU.

Where trial sites do not routinely collect quality of CPR data, these data will be collected for a subset of trial site participants using CPR cards, provided by the WCTU.

CE marked CPR cards, supplied by Laerdal Medical, will measure compression fraction, compression rate and depth. CPR cards are operated by switching on and placing centrally on the patient's chest. Chest compressions are then performed as usual. Quality of CPR data will be recorded during the resuscitation attempt but the card will not provide real-time feedback to the paramedics.

Up to 1,000 CPR cards will be distributed amongst trial sites. Trial trained paramedics will be taught how to use the CPR cards. Trial sites will use site specific processes to return used CPR cards from paramedics to site research teams. Site research teams will download data from the returned used CPR cards and provide the quality of CPR data securely to the WCTU.

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse events (AE)

An AE is: “Any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research, which does not necessarily have a causal relationship with the research”.

4.1.2 Adverse Reactions (AR)

An AR is defined as any untoward and unintended response to the study IMP (adrenaline). A causal relationship between the trial treatment and an adverse event is at least a reasonable possibility, ie the relationship cannot be ruled out.

4.1.3 Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Events (SUSARs)

An AE or AR is considered serious if it:

- 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 anomaly or birth defect
- Is an important medical condition

A SAE is not thought to be causally related to the research.
A SAR is thought to be related but is expected.
SUSARs are SARs that are unexpected i.e their nature or severity is not consistent with the Summary of Product Characteristics.

4.2 Reporting SAEs and SUSARs

Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation should NOT be reported. These include:

- Death
- Hospitalisation
- Persistent or significant disability or incapacity
- Organ failure

All events categorised as serious (SAE/SAR/SUSAR) must be reported to WCTU within 24 hours of becoming aware of the event.

All reports of SAE/SAR/SUSAR will be reviewed on receipt by the Chief Investigators and those that are considered to satisfy the criteria for being related to the IMP and unexpected will be notified to the Main REC, MHRA and sponsor within 7 or 15 days of receipt in accordance with regulatory requirements. Reports of SAE/SAR/SUSAR will also be reviewed by the DMC at their regular meetings, or more frequently if requested by the DMC Chair.

4.3 Procedures in case of Pregnancy

Known pregnancy at the time of the cardiac arrest is an exclusion criterion for this trial however should the patient later be known to have been pregnant at the time of cardiac arrest and trial intervention then the following will apply:

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. 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 was discontinued from the study.

All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE.

4.4 End of the Trial

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

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee (MREC)
- Mandated by the MHRA
- The TSC decides that recruitment should cease following recommendations from the DMC
- Funding for the trial ceases

The Main REC and MHRA will be notified in writing if the trial has been concluded or terminated early within 15 days.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act and WCTU SOPs.

5.1 Data Collection and Management

The case report forms (CRFs) will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator, ambulance services and Statistician.

Data from ambulance services will be entered into the trial database in anonymised format (identified by the arrest date and case number) for patients known to have died.

For survivors in hospital, personal identifiable information will be shared with WCTU, to allow future contact and follow-up. Handling of personal identifiable data will occur in accordance with WCTU SOPs.

Where we have not been able to collect data about the patients stay in hospital such as length of stay on ICU this will be collected from electronic datasets such as Intensive Care National Audit and Research Centre (ICNARC), Patient Episode Database for Wales (PEDW), and or Hospital Episode Statistics (HES), National Institute for Cardiovascular Outcomes Research (NICOR) and ONS mortality data. These data sets will also be used for the health economic analysis.

Survival status and health outcomes will be tracked through linkage (HSCIC) and hospital and/or GP records.

5.2 Database

The database will be set up by the Programming Team at WCTU and all specifications (i.e. database variables, validations checks, screens) will be agreed between the programmers, statistician and trial co-ordinator. The database will be tested and validated in accordance with the WCTU SOPs for secure data management.

5.3 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. Any paper data forms will be stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data will be stored in a secure area of the computer with access restricted to staff working on the trial. All databases containing identifiable information will be password protected. Any data that are transferred out of the secure environment (for example for statistical analysis, ICNARC, HES) will adhere to our unit SOPs.

5.4 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial. Electronic data sets will be stored indefinitely.

6. ANALYSIS

6.1 Statistical analysis

The primary analysis will be by intention to treat, comparing the outcomes between all participants randomised to adrenaline and all those randomised to placebo. The focus of the analysis will be on estimation of treatment effects and the uncertainty around them. A detailed statistical analysis plan will be developed by the trial statisticians and approved by the TSC and DMC.

Results will be presented as estimates of the treatment effect with 95% confidence intervals. Dichotomous outcomes (survival to 30 days, survived event, and survival to hospital discharge, 3, 6 and 12 months) will be analysed using logistic regression models, both unadjusted and adjusted for appropriate covariates. Survival and other time to event outcomes such as duration of hospital and ICU stay will be analysed using time to event techniques. Continuous outcomes (quality of life, cognition, anxiety/depression, posttraumatic stress) will be analysed by regression methods and the results presented as the difference in means between the groups and 95% confidence intervals. Modified Rankin Scale (a 7 category ordinal variable) will be analysed by ordinal logistic regression and the results will be presented using odds ratios and 95% confidence intervals. This will provide an increase in power over using a dichotomous outcome variable. Reporting of analyses will follow CONSORT guidelines.

The following exploratory analyses will be used to investigate potential modifiers of the treatment effect of adrenaline:

- Age
- Witnessed cardiac arrest versus not witnessed

- Bystander CPR versus no bystander CPR
- Type of initial rhythm (VF/VT, PEA, Asystole)
- Time of 999 call to administration of adrenaline
- Aetiology of cardiac arrest (presumed cardiac versus non-cardiac).

For categorical subgrouping variables we will fit interaction terms in logistic regression models to estimate the difference in treatment effects between the subgroups and the uncertainty around this. For continuous variables, we will fit the treatment-modifying factor as a covariate in regression models.

We will measure health related quality of life using EQ-5D at 3 and 6 months. We have selected 3 months for the timing of the initial measurement as studies indicate that neurological recovery plateaus from that time point. From the EQ-5D we can calculate health utilities for all participants, using standard tariffs. Patients who have died by 3 months will be attributed health utility of zero, and we will interpolate a value for any that die between 3 and 12 months. We will use methods of analysis developed by Goodacre et al 2012(47).

We will collect data on quality of CPR from across our trial sites and analyse all of the quality of CPR data collected.

6.2 Interim analyses

The DMC will monitor the accumulating outcome data, and one of their roles is to recommend cessation of recruitment if a clear result has been reached (i.e. if either adrenaline or placebo is clearly superior). We suggest that different thresholds of evidence for early termination are adopted if adrenaline or placebo being more effective, as it is likely that stronger evidence would be needed to change current practice (adrenaline use) if placebo is found to be superior. We therefore propose that interim analyses are conducted frequently in the early stages of the trial, so that, if adrenaline is superior, this can be detected early. Thus we will minimise any risks to patients while producing robust evidence that will change practice.

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

6.3 Economic Evaluation

An economic evaluation will be integrated into the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective (48). Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and six months post-randomisation. Resource utilisation data will be collected through four principal means: (i) use of trial interventions, concurrent treatments, mode and distance of initial transportation and subsequent transfers, will be estimated using the computerised data collection systems developed for the PARAMEDIC trial; (ii) detailed information on ITU resource utilisation and specific treatments (e.g. cardiovascular support, therapeutic hypothermia use) will be collected using bespoke trial data collection forms; this information will in turn be validated, and where necessary complemented, using information

collected from the Intensive Care Research National Audit Programme; (iii) information on subsequent hospital inpatient and day case admissions and outpatient visits will be collected though Hospital Episode Statistics; and (iv) trial participants or, where necessary, appropriate proxies will be asked to complete economic questionnaires profiling hospital readmissions and post-discharge health and social community care resource use at each time point of follow-up. For the purposes of a sensitivity analysis that will replicate the economic evaluation from a societal perspective, out-of-pocket expenses, and costs associated with lost productivity will also be measured in the economic questionnaires. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. A per diem cost for each level of hospital care, delineated by level of intensity, will primarily be calculated using national tariffs. However, primary research that uses established accounting methods may also be required to estimate costs unique to this trial. This may entail obtaining costs from NHS finance departments and apportioning these to different categories of patient using a 'top-down' methodology. Trial participating centres will be visited to ensure consistency in cost apportionments. The unit costs of community health and social services will largely be derived from national sources(49), although some calculations from first principles using established accounting methods may also be required]. Trial participants or, where necessary, appropriate proxies will be asked to complete the EuroQol EQ-5D-5L(50) and SF-12(51) measures at each time point of follow-up. In addition, health-related quality of life immediately prior to the critical illness will be retrospectively recalled at three months post-randomisation using the EQ-5D-5L and SF-12 by the trial participants themselves or, where necessary, appropriate proxies(52). Responses to the EQ-5D-5L and SF-12 will be converted into multi-attribute utility scores using established algorithms(53, 54).

An incremental cost-effectiveness analysis will be performed and expressed in the following terms: (i) incremental cost per additional survivor to 30 days post-cardiac arrest; (ii) incremental cost per additional neurologically-intact (mRS) survivor; and (iii) incremental cost per quality-adjusted life year (QALY) gained. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. Heterogeneity in the trial population will be explored by formulating a net-benefit value for each patient from the observed costs and effects, and then constructing a regression model with a treatment variable and covariates such as age, gender, duration of OHCA and study site. The magnitude and significance of the coefficients on the interaction between the covariates and the treatment variable should provide an estimate of the cost-effectiveness of adrenaline by sub-group. Due to the known limitations of within-trial economic evaluations(55) we will also construct a decision-analytical model to model beyond the parameters of the proposed trial the cost-effectiveness of adrenaline in this clinical population. Survival analysis models will be used to estimate life expectancy with and without adrenaline beyond the time horizon of the trial. Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Ethical conduct of the trial

The trial will be carried out in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Good Clinical Practice and applicable regulatory requirements.

The trial will be subject to the requirements of the Medicines for Human use Act 2004 (and amendment 2006) and approval is being sought from the Main REC, MHRA, CAG and R&D departments of participating NHS Trusts (a single SSI form is available for all Acute Trusts).

7.2 Sponsor

The University of Warwick will act as Sponsor for the trial.

7.3 Indemnity

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

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

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

7.4 Trial Timetable and Milestones

Table 2

	Month	Recruitment
Set-up	1-6	n/a
Pilot study	7-12	181
Recruitment	13-42	8,000
Follow up	43-48	n/a
Analysis	49-54	n/a

7.5 Administration

The trial co-ordination will be based at WCTU, University of Warwick.

7.6 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 TSC or Investigators, as appropriate.

7.7 Investigators Group

The Investigators team, comprising of the ambulance service teams, will meet regularly throughout the trial, either face to face, by teleconference or through other means of communication, to review the progress of the trial and discuss any issues in managing the trial.

7.8 Trial Steering Committee (TSC)

A TSC, consisting of several independent clinicians and trialists, lay representation, investigators and an independent Chair, will oversee the trial. Face to face meetings will be held at regular intervals determined by need but not less than once a year.

The TSC will take responsibility for:

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

7.9 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. During the period of recruitment into the trial, interim analyses of the accumulating data will be supplied, in strict confidence, to the DMC, along with any other analyses that the committee may request. The frequency of these analyses will be determined by the committee.

The DMC will advise the Chair of the TSC if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management. Following a report from the DMC, the Steering Committee will decide what actions, if any, are required. Unless the DMC request cessation of the trial the Steering Committee and the collaborators will remain ignorant of the interim results.

DMC meetings will also be attended by the Chief Investigator and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

Any publications relating to this trial or that may have an impact on the running of the trial will be reviewed by the DMC and fed back to staff through training.

7.10 Essential Documentation

A Trial Master file will be set up and held securely at the WCTU.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

8.1 Training

All ambulance clinicians participating in the trial will be trained at least once as detailed in section 2.10.5. It will not be possible to train all clinicians in GCP but general principles will be briefly covered during the training.

Principal Investigators, R&D leads, Research Paramedics and WCTU administration staff will be required to undergo GCP training and provide a CV to the WCTU. Any new staff to the trial within the WCTU administration team, or new Research Paramedics working within the ambulance service trusts will follow a thorough induction plan put together by the Trial Co-ordinator and relevant ambulance service.

Training will also be carried out for WCTU administration staff who may answer phone calls from patients or legal representatives 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.

8.3 Completeness of data

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

8.4 Visits to Sites

As per the WCTU monitoring plan, after the initial site initiation visit to each ambulance service and subsequent induction for each Research Paramedic, the Trial Co-ordinator(s) will have regular contact with the ambulance service trusts to identify any problems with compliance with the protocol, training, data collection, IMP accountability 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, at least one site visit will be made per year to meet with the trial team at each ambulance service and discuss any issues and check for consistencies.

The Trial Co-ordinator(s) 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

During the planning and development phase we have worked with the PPI members of the PARAMEDIC trial who contributed to the trial design and proposed follow-up systems. Specific contributions related to the selection of outcome measures, summary / presentation of research in

plain English. We held a community engagement event (supported by West Midlands South CLRN) in late November 2012 where we presented the scientific rationale behind this trial to a group of 280 lay-people who were interested in first aid. After preparing the talk in collaboration with one of our PPI representatives (John Long) to ensure concepts were presented in plain, understandable English, we delivered the presentation and addressed questions / queries from the group. We explained the concept of short term and longer-term outcomes and briefly sought community views about priorities for outcomes and their views on a trial of adrenaline for out of hospital cardiac arrest. We received responses from 243 participants. Ninety-five percent of respondents prioritized long-term survival over short-term survival (hours to days). Participants broadly agreed there was a need for further research about adrenaline as a treatment for cardiac arrest (86% agreed, 8% neither agree nor disagreed, 6% disagreed).

Our PPI partners will play key roles in the management of the research. John Long, a former senior police officer, with extensive experience of working with charities dedicated to reducing death from cardiac arrest will be a member of the trial management group and lead PPI representative. In this role John will liaise with our other PPI partners. We propose to include two PPI representatives in the TSC. We will provide regular update on progress with the trial to our Critical Care Resuscitation Advisory Group (CRAG). CRAG is our established user representative group who meet on a quarterly basis to contribute to and receive updates on our various projects. The group consists of approximately 40 PPI members.

In addition the WCTU team formed a PPI group comprised of 8 members of the public, to give advice on the content and distribution of patient and public facing documents. The group was put together through the University of Warwick's UNTRAP group and includes a cross section of age, gender, religion and experience. There is also variety of preferences for communications i.e. use of the internet.

The trial PPI group met face to face at the University of Warwick for the 1st meeting before the start of the pilot (August 2014). We wanted to seek their views on the general concept of the research in this area and to ensure the patient facing documents were sensitive, clear and understandable.

We also sought their advice on the trial communication strategy (ways in which information about the trial can be shared within relevant communities) and wording of the press release to reflect the key messages are understandable and clear. Documents were sent out to the group members by email, before the meeting, for them to review. Several of the comments made were taken forwards and were fed back to the group at the second meeting in May 2015, towards the end of the pilot. This second meeting was to discuss the revised communication strategy, the new posters and leaflets and the website in order for us to ensure the key messages are clear.

We will continue to meet at least annually thereafter and on an ad hoc basis when a review or consultation is required.

Information about the trial will be available on our website.

10. DISSEMINATION AND PUBLICATION

We will continue to build links with key stakeholder group (e.g. Ambulance Service Medical Directors, College of Paramedics, Resuscitation Council UK, Intensive Care Society, Patient / Public Involvement Groups). We will continue to publish editorials and review articles related to adrenaline use in cardiac arrest. The purpose of these activities are to highlight the uncertainty of current treatment with

adrenaline and to generate and sustain interest from the clinical community so that the trial results will be eagerly anticipated.

We will publish the trial protocol and final trial results in high impact, open access peer reviewed journals. In addition, we will present the results at scientific conferences and to ambulance services (National Ambulance Service Medical Directors and Joint Royal College Ambulance Liaison Committee).

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the WCTU team, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines(56). The main publications will be the report to the funding body (HTA Monograph) and a journal publication. In addition, the results will be presented at international conferences. This will ensure that the results are communicated rapidly to those who will put them into practice. We will inform the ILCOR to ensure the results will be incorporated into national and international resuscitation guidelines via existing guideline development groups, which include several of the applicants.

We will incorporate the findings of the trial into relevant review articles and ensure the findings of the trial are available through NHS Evidence (Clinical Lead Co-inv Quinn). We will work with our Marketing and Communication team to develop a strategy for communication with the media (television, radio, newspaper etc) to enhance communication of the trial results to patients / participants.

We will produce a lay summary of the trial results with our public and patient involvement partners. This will be disseminated through our press officer, user groups, websites and INVOLVE database to participants of the trial who indicated they wanted to know the results.

We expect the output from this trial will impact international CPR practice. There are established pathways through which advances in resuscitation science can be rapidly implemented into practice.

We will ensure that the results of this trial are fed into the ILCOR evidence assessment and guideline process. ILCOR run a 5 yearly review of resuscitation science from which international CPR guidelines are created. There is good evidence of penetration of these guidelines into clinical practice within 1-2 years of their publication(57).

Guidelines used by the NHS are based on recommendations from the Resuscitation Council (UK) and are implemented within NHS Ambulance Trusts through the JRCALC.

We anticipate that the impact of this trial will be sufficient to determine future policy in this area. We are well positioned to facilitate this research impacting on future international guidelines. Co-investigator Jacobs is Co-chair of the International Liaison Committee on Resuscitation. Perkins, Finn, Nolan and Deakin either co-chair or are members of ILCOR working groups. Perkins, Nolan and Deakin contribute to the NHS guidelines through the Resuscitation Council (UK).

A policy for authorship of trial publications will be drafted and agreed by the investigators early in the trial, in accordance with the WCTU Standard Operating Procedures.

11. FINANCIAL SUPPORT

The trial is funded by the NIHR Health Technology Assessment Programme, grant number 12/127/126.

12. PROTOCOL AMENDMENTS

- Amendment 1 – Minor changes to Patient Information Sheet, consent forms, cover letter and OK to ask poster following comments from Confidentiality Advisory Group (CAG)
- Amendment 2 – Addition of Welsh hospitals as sites in order to obtain R&D approvals
- Amendment 3 – Addition of English hospitals as sites in order to obtain R&D approvals
- Amendment 4 – Clarification to REC that prisoners would not be excluded from the trial in the event that they have a cardiac arrest
- Amendment 5 – Update to opt-out procedures and communication strategy
- Amendment 6 – Update to protocol following the pilot
- Amendment 7 – Addition of 1 English hospital to list of sites
- Amendment 8 – Revision of IMPD to confirm 12 month shelf life
- Amendment 9 – letter to GP to obtain mRS score
- Amendment 10 – Addition of 4 English hospitals to list of sites

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