



PROTOCOL

Prehospital Randomised Assessment of a Mechanical Compression Device In Cardiac Arrest

(PARAMEDIC)

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
CPC	Cerebral Performance Category
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonisation
JRCALC	Joint Royal College Ambulance Liaison Committee
LREC	Local Research Ethics Committee
LUCAS	Lund University Cardiopulmonary Assistance System
MMSE	Mini Mental Health State Examination
MRC	Medical Research Council
MREC	Main Research Ethics Committee
MRIS	Medical Research Information Service
NICE	National Institute for Health and Clinical Excellence
NRES	National Research Ethics Service
PTSD	Post traumatic stress disorder
QOL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROSC	Return Of Spontaneous Circulation
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Sudden cardiac death is a major cause of death and morbidity in the Western world. In Europe, approximately 700,000 people sustain a cardiac arrest in the community each year. Only about 5% of these patients survive to hospital discharge. Many survivors have acceptable health-related quality of life, which emphasises the importance of optimising early treatments aimed at achieving return of spontaneous circulation. Effective treatments for cardiac arrest are extremely limited and represent a major un-met health need.

In the UK, a national audit of ambulance services identified 57,345 out of hospital cardiac arrests. Resuscitation was attempted in about 44% of these cases, with about 15.6% surviving to hospital admission. There is substantial subsequent mortality of those who survive to hospital, and survival to hospital discharge is about 5%. The cost to the NHS of out of hospital cardiac arrest management is about £320m/year.

Following sudden cardiac arrest, effective circulation to the vital organs ceases within a matter of seconds, followed by irreversible cell death within minutes. There is clear evidence that early cardiopulmonary resuscitation (CPR) including chest compression and defibrillation improves outcome.(1) In addition, the quality of chest compressions has a significant impact on the likelihood of survival. Manual chest compressions achieve at best approximately 30% of the normal cardiac output, and inadequate compression depth or rate, and interruptions in chest compressions all adversely affect survival. There is good evidence that it is extremely difficult to maintain manual CPR of sufficient quality. For example, a recent study of 176 out-of-hospital resuscitation attempts found that chest compressions were only given for 52% of the resuscitation time, and only 28% of compressions adhered to international guidelines.(2) The finding of poor quality CPR and frequent and prolonged interruptions in chest compression is perhaps not surprising; paramedics attending a cardiac arrest need to deliver a number of interventions within the first few minutes of arrival (defibrillation, airway management, chest compression, intravenous access), inevitably leading to significant interruptions in compressions. Rescuer fatigue also reduces chest compression quality as early as 1 minute after commencing chest compression.(3) CPR quality is further impaired during transfer of the patient to hospital where a single paramedic is tasked with compression, ventilation, defibrillation and any other interventions, in a moving vehicle.(4)

Because of the problems with manual chest compression, several mechanical devices have been proposed (see section 1.2). These have several potential advantages; they are able to provide compressions of a standard depth and frequency for long periods without interruption or fatigue, and they free emergency medical personnel to attend to other tasks.

The LUCAS (Lund University Cardiopulmonary Assistance System) is a mechanical device that provides automatic chest compressions, manufactured in Sweden by JOLIFE AB (see section 2.11.1 for details). It delivers sternal compression at a constant rate to a fixed depth by a piston with the added feature of a suction cup that helps the chest return back to the normal position. It compresses 100 times per minute to a depth of 4-5cm, in adherence with International scientific guidelines on CPR.(5) It is easy to apply, stable in use, relatively light in weight (7.8 kg), and well adapted to use during patient movement on a stretcher and during ambulance transportation. The device is CE marked and has been on the market since 2002 in Europe. Detailed descriptions of the device and experimental data from animal studies showing increased cardiac output and cortical cerebral flow compared to manual standardised CPR have been published.(6)

LUCAS was introduced into a small number of ambulance services in the UK several years ago, despite the absence of evidence of its effectiveness from randomised trials.(7) It was subsequently withdrawn from routine use by several of the services due to lack of evidence about safety and efficacy and is now used only under restricted conditions. In the absence of evidence of clinical or cost effectiveness and the presence of some concerns regarding safety, the Joint Royal College Ambulance Liaison Committee (JRCALC), in discussion with the Department of Health, identified the need for large scale clinical trials to evaluate the device.(8) Until such studies are completed, no further new purchases of the device are recommended by JRCALC. A briefing note commissioned by NICE concluded; “there is therefore an urgent need to evaluate this technology to discover whether it is effective and cost-effective in improving survival after cardiac arrest”. The need for a definitive trial is reinforced in the International Liaison Committee for Resuscitation analysis of knowledge gaps in resuscitation.(9)

Widespread adoption of LUCAS would be expensive, as the cost of each unit is around £7,000, and the running costs in one small ambulance service (Staffordshire) exceed £40,000 per year. Hence, economic evaluation is needed alongside the trial.

1.2 Existing knowledge

No large randomised controlled trials (RCT) evaluating the LUCAS device have yet been published. The only RCT evidence that exists is from one pilot trial that has been published in abstract form, once as a preliminary report (51 patients) and once as the completed pilot study (149 patients). (10, 11) This study was too small to give any clear results. Evidence from non-randomised observational studies is also very limited; one study, conducted in Sweden, found no advantage to LUCAS in terms of return of circulation, survival to hospital or survival to discharge, but the sample size of this study (328) was small.(12) A case series of 100 patients(13) and several case reports have suggested that LUCAS may improve survival of some patients.(14-17)

There is some evidence that LUCAS may be effective from the results of audits in the UK ambulance services where it is in use. For example, in Staffordshire, where LUCAS is in routine use, 27% of patients survived to hospital in 2005-6(18), compared with a national figure of 15.6% (2006). However, these data are from routine clinical practice; the accuracy of the data is unknown and may be poor, and they may be subject to uncontrolled biases and errors. Moreover, increased survival rates may be due mainly to shorter response times or other differences in care, rather than use of LUCAS.

A recent review conducted by the Aggressive Research Intelligence Facility (ARIF) at the University of Birmingham in 2006 concluded that there is no high-quality clinical research on the LUCAS device(19) and another systematic review conducted by the investigators and completed in Jan 2007, similarly failed to identify any high-quality evidence to support the device's use.

Other mechanical compression devices have been developed, but so far there is no clear evidence that any of them improves survival. The main alternative to LUCAS, AutoPulse (Zoll Medical Corporation, Chelmsford, MA), uses a different system, a load-distributing band around the chest, to provide chest compression. An RCT of this device in North America was halted early due to safety concerns, but suggested that the device conferred no benefit or possibly reduced survival to hospital discharge.(20) Moreover, neurological outcomes were worse in the mechanical compression group: 3.1% of the mechanical compression group survived with good neurological outcome (12/391) compared with 7.5% of the control group (28/371). A protocol for a Cochrane review of mechanical compression devices has recently been published(21). This has identified four trials, none of which evaluated LUCAS. The studies were generally of poor quality and only one reported

outcomes to hospital discharge (L.J. Morrison, personal communication). The reviewers concluded that at present there is insufficient evidence to determine whether mechanical chest compression is associated with benefit or harm.

A Cochrane review of a manually driven (as opposed to mechanical) active compression/decompression device found more frequent severe neurological damage in survivors of CPR (RR 3.11 [95% CI 0.98- 9.83])(22), highlighting the importance of measuring neurological outcomes after cardiac arrest: the goal of an out-of-hospital resuscitation attempt is for the patient to survive with their pre-arrest level of function intact.

Few studies have evaluated adverse effects of LUCAS, but one letter to a journal drew attention to high rates of chest injuries identified in patients who had not survived attempted resuscitation using LUCAS.(23) A post-mortem series of 47 cases where the LUCAS device was deployed found similar patterns of injuries to a matched group receiving standard CPR.(24) However, chest injuries are expected as a result of CPR, and a higher rate of injuries caused by LUCAS would be of little importance unless this translates into a change in more substantive outcomes such as increased mortality or disability, or an increase in duration of hospitalisation.

1.3 Ongoing research

A European RCT of LUCAS (LINC trial, n=2,500 clinicaltrials.gov NCT00609778), sponsored and overseen by the device manufacturers and co-ordinated by Uppsala Clinical Research Centre, Sweden, started recruitment in 2008. The LINC trial differs from PARAMEDIC in several respects. The control arm will receive standard resuscitation according to current guidelines, as is the case in our trial. However, the LUCAS arm of their trial will differ substantially from both our proposal and current international resuscitation guidelines. In addition to using the LUCAS device, the experimental intervention will include the use of blind shocks without ECG analysis; delaying adrenaline for 9 minutes after arrival on scene, and giving 3 minutes of compression/ventilations between shocks. The primary outcome for LINC is four-hour survival. The secondary outcomes include survival and neurological status (CPC score) at hospital discharge, which will allow subsequent comparisons and meta-analysis of the main trial outcomes. There are no other trials registered on the International Standard Randomised Controlled Trial Number (ISRCTN) database.

1.4 Need for a trial

A clinical trial to investigate the clinical and cost-effectiveness of mechanical chest compression devices has been called for by the JRCALC, DH Emergency cardiac care board, NICE, Cochrane reviewers and the International Liaison Committee for Resuscitation. The need for further research on the use of compression devices has also been registered with the NHS database of uncertainties about the effects of treatments (DUETS).(25)

1.5 Good Clinical Practice

The trial will be carried out in accordance with the Medical Research Council (MRC) Good Clinical Practice Guidelines(26), and applicable UK legislation.

2. TRIAL DESIGN

2.1 Trial summary

PARAMEDIC is a cluster randomised controlled trial and economic evaluation. We have chosen to use a cluster randomised design because an individually randomised design would have a significant danger of a high level of contamination among the manual compression arm. In an individually randomised design, all vehicles taking part in the trial would have to carry a LUCAS device, and there would be a strong possibility that it would be used for patients allocated to manual compression, especially if the perception of paramedics was that LUCAS made chest compression easier and allowed them to carry out other tasks more effectively.

We will use vehicles (ambulances and rapid response vehicles (RRVs)) as randomisation units. Vehicles will be randomly allocated before the start of recruitment to carry LUCAS (LUCAS arm) or no LUCAS (manual compression arm). Patients will be eligible if they are in cardiac arrest in the out-of-hospital environment, the first ambulance resource is a trial vehicle, are aged 18 years or over, and a resuscitation attempt is started. Exclusions are cardiac arrest as a result of trauma, and known or clinically apparent pregnancy. Interventions will be either use of LUCAS for chest compression during resuscitation, or standard manual chest compression (control). Outcomes are survival to hospital, survival to 30 days, 3 months and 12 months, and neurologically intact survival to 3 months (survival with Cerebral Performance Category (CPC) score 1 or 2). All survivors will be followed up at 3 months, to measure health-related quality of life, and at 12 months, to evaluate cognitive status (mini-mental state examination), post traumatic stress (PTSD civilian checklist) and anxiety and depression (Hospital Anxiety and Depression Scale).

2.2 Objectives

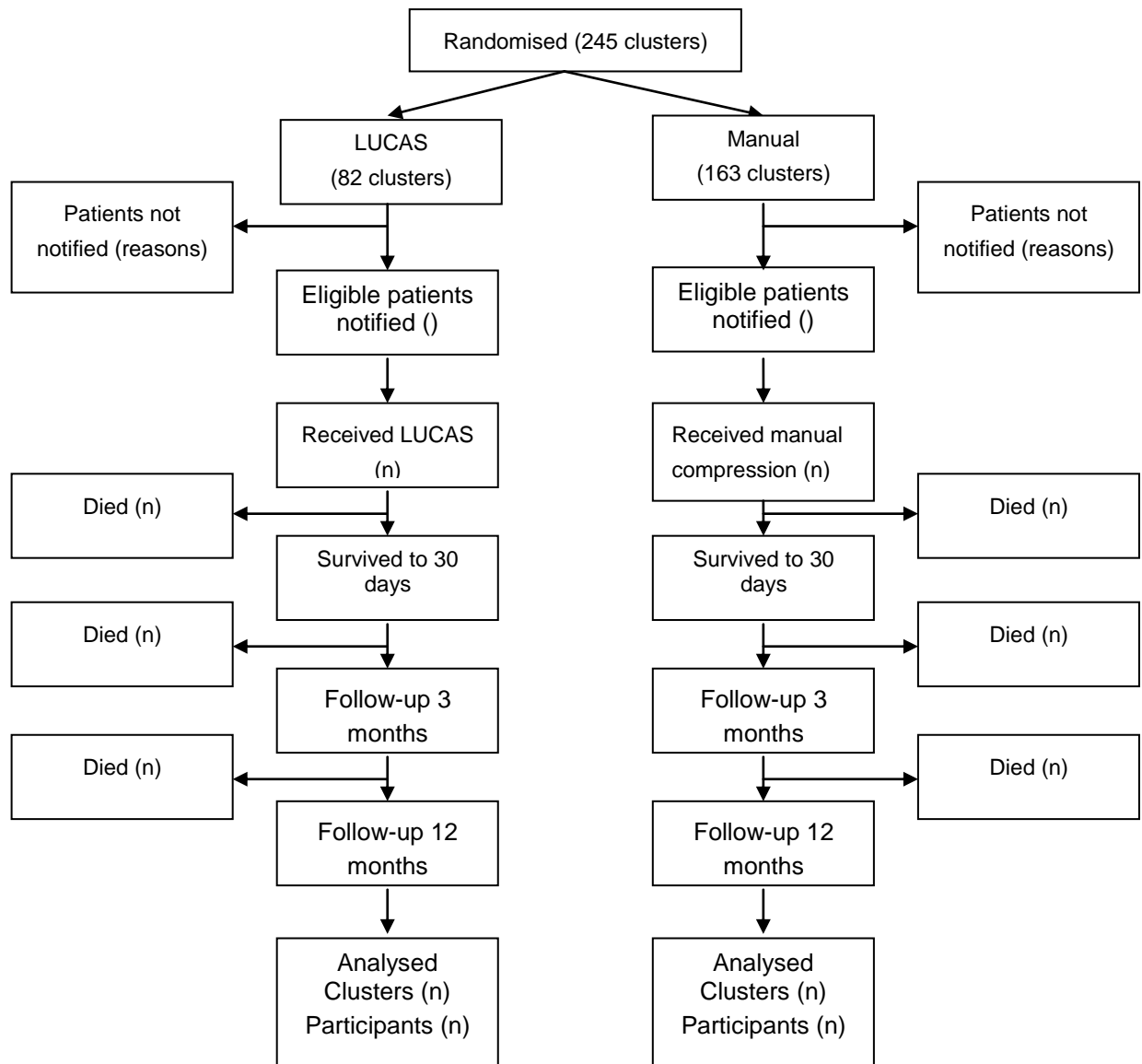
2.2.1 Primary objective

The primary objective of this trial is to evaluate the effect of using LUCAS rather than manual chest compression during resuscitation by ambulance clinicians (paramedics, technicians ECA etc) after out of hospital cardiac arrest **on mortality at 30 days after the event.**

2.2.2 Secondary objective

Secondary objectives of the study are to evaluate the effects of LUCAS on survival to 12 months, cognitive and neurological outcomes of survivors and cost-effectiveness of LUCAS.

Figure 1. Flow chart for PARAMEDIC trial



2.3 Outcome Measures

Primary outcome:

Survival to 30 days post cardiac arrest.

Secondary outcomes:

1. Survived event (sustained return of spontaneous circulation (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. Survival to 3 and 12 months
4. Health related quality of life at 3 and 12 months (SF12 and EQ-5D)
5. Neurologically intact survival to 3 months (survival with CPC score 1 or 2)
6. Cognitive outcome at 12 months (Mini Mental State Examination (MMSE))
7. Anxiety and depression at 12 months (Hospital Anxiety and Depression Scale (HADS))
8. Post Traumatic Stress at 12 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⁽²⁷⁾ will be reported, and long-term follow-up will be at 12 months, as recommended by the Utstein guidelines. We do not propose to measure the incidence of injuries resulting from CPR, for three reasons: first, they are of little importance unless they result in differences in more substantive outcomes such as survival or duration of hospitalisation; second, they are difficult to measure and classify, and may not be detected reliably; third, organising injury data collection from a large number of hospitals would add significant organisational complexity to the trial, for little benefit.

The CPC score is a 5-point scale for describing the neurological outcome after cardiac arrest, and is recommended by the Utstein guidelines. There is a generally accepted split into good neurological outcome (CPC 1-2) and poor outcome (CPC 3-5). The definitions of the categories are:

- CPC 1. Good cerebral performance: conscious, alert, able to work,
- CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
- CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
- CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria.
- CPC 5. Brain death

However, recent studies have demonstrated that this score may be insensitive to some of the more subtle, but nevertheless important longer term neurocognitive and functional impairments experienced by survivors of cardiac arrest.^(28, 29) The spectrum of impairment of health related quality of life following cardiac arrest includes memory and cognitive dysfunction, affective disorders and post traumatic stress disorder (PTSD).⁽²⁹⁾ The number of patients expected to survive to hospital discharge is anticipated to be in the region of 200-300, which will allow more intensive follow-up. We will use four clinical outcome measures: SF-12 is a standard quality of life measure that is short and easy to complete. The PTSD Civilian Checklist (PCL-C)⁽³⁰⁾ is a 17-item 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 Hospital Anxiety and Depression Scale (HADS) is a 14-item self administered questionnaire which has been previously used successfully to measure affective disorders in cardiac arrest survivors.(31) The mini-mental state examination (MMSE) measures cognitive impairment.(32) In addition the EQ-5D will be used as a health utility measure for the health economic analysis.

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.(33)

2.3.1 Safety

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

2.4 Power and Sample Size

2.4.1 Incidence of primary outcome

There are few data on the incidence of survival after cardiac arrest, and most data refer to survival to hospital discharge rather than survival to 30 days. However, as most mortality will occur in the first days after cardiac arrest, we expect survival to hospital discharge and to 30 days to be similar. A systematic review, published in 2005,(34) has summarised all European data. The overall incidence of survival to hospital discharge was 10.7%, with 21.2% survival to discharge for patients with an initial rhythm of VF. This review included eight studies from the UK, in which the mean survival to hospital discharge was 8.1% overall and 17.7% for patients with initial VF rhythm. Data on survival to discharge from audits of UK ambulance services are limited, because few ambulance services collect outcome data for patients beyond admission to hospital. Figures from the London Ambulance Service (2006-7) indicated a survival rate to discharge of 5.2% (95% CI 4.4% to 6.0%).(35) National audit data for England (2006) indicate that the proportion of patients in whom resuscitation is attempted that have ROSC at admission to hospital varies between 10% and 26% for different ambulance services.(18) The overall national figure (2004-2006) is 14 to 16%. Estimates of mortality in hospital vary from 50% to 70%, hence the incidence of survival to discharge is expected to be between 4.5% and 8%.(36) A reasonable conservative estimate of survival to 30 days is 5%, and we have used this value in the sample size calculations.

2.4.2 Intracluster correlation coefficient

No data currently exist from which a relevant intracluster correlation coefficient (ICC) for this trial can be calculated. We have therefore assumed a conservative value of 0.01 for the sample size calculation. We expect that, because the LUCAS and manual compression clusters will recruit from the same geographical areas, and hence the same populations, the ICC will be low. The value of the ICC will be monitored at interim analyses by the DMC, who will make recommendations for adjustments to the required sample size.

2.4.3 Cluster size

Predicting the expected cluster size during the trial is difficult because of expected changes in the vehicles in service and the proportion of eligible cardiac arrests they are likely to attend. Moreover there is likely to be considerable variation in the number of cardiac arrests attended by each vehicle (i.e. variation in cluster size). Data from West Midlands Ambulance Service suggest that each vehicle

would attend around 10-20 cardiac arrests per year; allowing for non-resuscitations and periods off the road, a reasonable estimate of the cluster size over a 2 year recruitment period is 15.

2.4.4 Sample size required

The required sample size is sensitive to variation in several parameters that are currently not precisely known, including the incidence of the primary outcome in the manual compression group and the ICC. We aim to be able to detect, with 80% power, an increase in the incidence of survival to 30 days from 5% in the manual compression group to 7.5% in the LUCAS group (a risk ratio of 1.5). An increase in survival from 5% to 7.5% corresponds to a number needed to treat of 40, or one extra life saved per 40 resuscitation attempts. This would translate into about 625 lives saved per year in the UK. In an individually randomised trial this would require 2942 participants. Allowing for clustering, assuming an ICC of 0.01 and a cluster size of 15, this would require 224 clusters if using a 1:1 randomisation ratio (112 LUCAS, 112 manual; 3360 participants in total).

Because the number of LUCAS devices available to the trial is limited, it is more efficient not to use a fixed 1:1 randomisation ratio (see Section 2.5.1), but to randomise a number of LUCAS devices among all of the vehicles at each ambulance station. This allows inclusion in the trial of all cardiac arrests attended by vehicles from that station. Table 1. below gives the numbers of clusters required for 80% power to detect the difference specified above, with different randomisation ratios and cluster sizes.

Table 1.

Cluster size	Ratio LUCAS: standard	Clusters required			Total number of participants
		Total	LUCAS	standard	
14	1:1	238	119	119	3332
	1:2	260	87	173	3640
15	1:1	224	112	112	3360
	1:2	245	82	163	3675
16	1:1	212	106	106	3392
	1:2	231	77	154	3696
18	1:1	192	96	96	3456
	1:2	210	70	140	3780
20	1:1	176	88	88	3520
	1:2	192	64	128	3840

Our target will be to randomise 82 LUCAS clusters and 163 standard care clusters, and a total sample size of 3675 participants. We expect to determine the primary outcome for close to 100% of trial participants, so no inflation of the sample size to allow for losses to follow-up of individual participants is proposed. With this sample size, the 95% confidence interval around an estimated treatment effect of a RR of 1.50 would be 1.14 to 1.94, including adjustment for clustering.

Within this sample size we expect around 25% of patients to have an initial rhythm of VF (approximately 920 patients). This subgroup is expected to have significantly higher survival than the rest of the population, of around 15%. The number in this subgroup will be sufficient to show an increase from 15% to 22.8% (RR 1.52) with 80% power, allowing for clustering.

The DMC will monitor the values of all parameters of the sample size calculation at interim analyses and will advise on any necessary modifications to the sample size.

We will concentrate recruitment in urban areas, because each vehicle is likely to attend more cardiac arrests. We plan to exclude the area of the former Staffordshire Ambulance Service from the trial because LUCAS is currently routinely used there and has been for several years.

2.5 Eligibility Criteria

2.5.1 Eligibility for clusters

All vehicles that are in service at each participating ambulance station and may attend eligible patients will be included in the trial and randomised to one of the trial arms, before the start of recruitment.

Because the number of LUCAS devices is limited, it will be inefficient to randomise vehicles in a 1:1 ratio. This would entail some vehicles at each station not contributing to the trial, and hence non-inclusion of potentially eligible cardiac arrests. Costs of additional standard care clusters are minimal, so we will ensure that all eligible cardiac arrest contribute to the trial by allocating a number of LUCAS devices to each participating station, and randomly allocating them among all of the vehicles that will attend cardiac arrests. The number of vehicles available will vary and it will not be possible to ensure that allocation is in any precise ratio, but we will aim for the ratio of LUCAS to standard care vehicles to be approximately 1:2. An additional major benefit of this procedure is that the trial will be simpler for ambulance crews, because all vehicles at each station will be participating in the trial.

To maximise the efficiency of the trial, recruitment will be concentrated predominantly in urban areas, where each vehicle will attend a higher number of cardiac arrests per year. This will avoid the costs of supporting clusters in rural areas that will be able to recruit very few patients, will increase the size of clusters and will increase the survival rate for the trial population, by omitting patients who cannot be reached quickly and have very low chance of survival. This will help to improve power to detect a difference between the LUCAS and manual compression arms.

2.5.2 Eligibility for individual patients

Patients will be eligible if all 4 of the criteria below are met:

1. they are in cardiac arrest in the out of hospital environment;
2. the first ambulance resource is a trial vehicle;
3. resuscitation attempt is initiated by the attending ambulance clinicians, according to JRCALC guidelines;
4. the patient is known or believed to be aged 18 years or over.

Exclusion criteria will be:

1. cardiac arrest caused by trauma
2. known or clinically apparent pregnancy

All patients who have out of hospital cardiac arrest in whom a resuscitation attempt is initiated will be included in the trial. The JRCALC Recognition of Life Extinction (ROLE) guidelines, which are already in use in the West Midlands and Scottish Ambulance Services, will be applied to

determine patients for whom a resuscitation attempt is inappropriate. This is the case when there is no chance of survival, the resuscitation attempt would be futile and distressing for relatives, friends and healthcare personnel and where time and resources would be wasted undertaking such measures. When any one or more of the following conditions exist, resuscitation and enrolment in the trial will not take place.

1. massive cranial and cerebral destruction
2. hemicorporectomy
3. massive truncal injury incompatible with life (including decapitation)
4. decomposition/putrefaction
5. incineration
6. hypostasis
7. rigor mortis
8. A valid do not attempt resuscitation order or an Advanced Directive (Living Will) that states the wish of the patient not to undergo attempted resuscitation
9. When the patient's death is expected due to terminal illness
10. Efforts would be futile, as defined by the combination of **all three** of the following being present (a) More than 15 minutes since the onset of collapse (b) no bystander CPR prior to arrival of the ambulance (c) asystole (flat line) for >30 seconds on the ECG monitor screen. Exceptions are drowning, drug overdose/poisoning, trauma.
11. Submersion of adults for longer than 1 hour

LUCAS cannot be used if patients are too large or too small; the device fits patients with a sternum height of 17.0 to 30.3 cm and a chest width of less than 45cm. However, patient size will not be an exclusion criterion because it will be impossible to apply correctly to the manual compression group, hence potentially introducing bias. Moreover, it is appropriate to include the small proportion of patients that are too large or too small for LUCAS in the trial, in accordance with intention-to-treat principles. The trial will estimate the impact of LUCAS on the survival rate among the whole cardiac arrest population. In one Swedish study,(12) only 3/159 patients (1.9%) were found to be too small or too large for LUCAS. We therefore anticipate that there will be only a small number for whom LUCAS cannot be used, especially as LUCAS-2 accommodates larger patients than the LUCAS version 1 that was used in the Swedish study.

Treatment allocation of each individual participant will be determined by the first trial vehicle to arrive on scene. If this is a LUCAS vehicle, the patient will be included in the LUCAS arm, and if it is a non-LUCAS vehicle (control), the patient will be in the manual compression arm. If the trial vehicle is not the first ambulance service vehicle to arrive on scene i.e. an ambulance or RRV which is not part of the trial (not randomised) has already arrived and commenced resuscitation, the patient will not be included in the trial. If the first response on scene is a community responder or other response, then the patient will be included and their allocation will be determined by the first trial vehicle to arrive, providing that continued resuscitation is indicated.

2.6 Ethical considerations

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

Treatment (in the form of CPR) must be started immediately in an attempt to save the person's life. 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 treatment.

Conducting research in emergency situations where a patient lacks capacity is regulated by the Mental Capacity Act (2005) for England and Wales and the Adults with Incapacity Act (2000) for Scotland. The PARAMEDIC trial has been approved in accordance with these requirements by the Coventry Research Ethics Committee (England and Wales) and Scotland A Research Ethics Committees.

In England and Wales a patient will be considered to have been enrolled in the trial at the time of their cardiac arrest if they meet the eligibility criteria and are attended by a trial vehicle. Consent will be sought to continue with follow-up.

In Scotland, the Adults with Incapacity Act (2000) does not permit research with patients that lack capacity unless consent is obtained. The Ethics committee noted that both forms of resuscitation (standard CPR and LUCAS CPR) were currently being used by ambulance services in the UK as part of routine clinical care. On this basis they determined that the research element effectively began with the follow-up phase and consent was only required at this point.

2.7 Approaching survivors

The nature of the condition means that the majority (85-90%) of people in the study will not survive. Of those patients admitted to hospital alive the majority (approximately 80%) will be comatose and admitted to an intensive care unit (and thus remain incapacitated). Following admission to intensive care approximately half of the people that initially survive die without regaining capacity (on average within 48 hours). The average duration of hospital stay for survivors is 18 days.

The timing of the approach is important and needs to balance the need to inform at an early opportunity while determining as accurately as possible which patients have died, to avoid unnecessary distress to relatives by approaching deceased patients. Pilot work for this trial has established that it is not possible for ambulance services to determine with sufficient accuracy which patients have died, so the procedure has been revised, based on the procedures of the ICON study.

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 may include contacts with hospitals, GP and local Registrars of Births and Deaths.

If a patient is not known to have died, their clinical and contact details will be sent to the study co-ordinating centre. Staff at the co-ordinating centre will check the status of each potential survivor with the Medical Research Information Service (MRIS) approximately six weeks after their cardiac arrest. This timing of approach should ensure that the majority of deaths will have been included in the MRIS database. All survivors will be flagged on the MRIS database and we will be informed if they die subsequently.

After these checks, if someone is still believed to be alive the co-ordinating centre will contact them at their home address by letter to provide information about the study and the follow-up, and notify them that a member of the study team will contact them in 1-2 weeks to discuss the study and seek consent for follow-up. This second contact will give the participants an opportunity to discuss the study and, if they are happy to proceed, a 3-month follow-up appointment will be made. The consent form may be either returned by post or can be signed at the 3-month follow-up visit.

In the event that the co-ordinating centre is notified (or have reason to believe) that a patient lacks capacity, an approach will be made to their general practitioner in order to establish if the patient has capacity to consent. In the event that a patient lacks capacity to consent we will seek the views of a personal consultee in order to establish the patient's wishes. If a personal consultee cannot be identified a carer (un-connected with the study) will determine if the patient would have been likely to consent to follow-up.

People that do not survive: It will not be possible to provide information to or obtain informed consent for follow-up from non-surviving patients. Due to the nature of the condition (cardiac arrest) this will be the case for the majority of participants (up to 95%). We have carefully considered the benefits and burdens of approaching the relatives of the deceased to inform them of their deceased relative's participation in the clinical trial. We have discussed this in detail with our clinical ethicist and patient representative. The advantages of informing next of kin are that the process of trial recruitment is open and transparent. However, knowledge of the trial participation after the event may 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. On balance we consider that the burden of imparting this information will outweigh the potential benefit. This assessment is informed by our local experience of informing relatives of non survivors during an in-hospital CPR study and the experience from an American trial of a similar intervention (ASPIRE), in which it was found that some families of non-survivors found information about their relative's participation in the trial distressing, and this part of the trial was changed for this reason.

2.8 Informed Consent

1-2 weeks after the initial contact, a research nurse/paramedic will contact the participant, by telephone if possible. They will answer any of the participant's questions about the study and seek consent for on-going follow-up. If the participant is happy to continue in the study, an appointment for the 3-month follow-up visit will be made. The participant may either return the signed consent form by post, or it can be signed at the 3-month visit.

2.9 Randomisation

Clusters (ambulance service vehicles) will be randomised to LUCAS or manual compression by the study statisticians before the start of recruitment. Randomisation will be performed using a method with secure allocation concealment that cannot be changed once allocated, and will allocate the vehicles at each station to LUCAS or manual chest compression in approximately a 1:2 ratio. If new vehicles are brought into service at participating stations during the recruitment period, these will also be randomised.

We aim to include all eligible patients attended by a participating vehicle during the trial recruitment period. The attending ambulance clinicians will determine whether a resuscitation attempt is appropriate, according to the JRCALC guidelines.

2.10 Protection against bias

2.10.1 Cluster design

One of the major potential sources of bias in cluster randomised trials is inclusion of different patients in the arms of the trial. This can arise where a large proportion of potentially eligible patients are not included in the trial, and the probability of inclusion is related to the intervention. In this trial we aim to identify and include close to 100% of the eligible patients, using a

combination of methods for identifying eligible patients, including direct notifications by ambulance clinicians and review of routine ambulance service data.

2.10.2 Threshold for resuscitation

Because ambulance clinicians delivering the interventions will not be blinded, there is a possibility that bias could be introduced by different thresholds for resuscitation between the LUCAS and standard care arms. If they believe strongly that LUCAS is effective, some of them may attempt resuscitation in the LUCAS arm of patients who have no chance of survival, and for whom a resuscitation attempt is therefore inappropriate. This would result in a group of patients with very low probability of survival being recruited to the LUCAS arm but not the standard care arm, potentially masking any beneficial effect of LUCAS. We will use several strategies to prevent this bias from occurring, to detect it if it happens, and to correct it if necessary.

First, the criteria that are used to determine whether a resuscitation attempt is appropriate, and hence whether the patient is eligible, are as objective as possible. The JRCALC Recognition of Life Extinct (ROLE) criteria are currently used by all participating ambulance services to determine when a resuscitation attempt is inappropriate, and this will continue in the trial (see 2.5.2). Ambulance clinicians will therefore be familiar with the application of these criteria, and no change of practice will be needed during the trial. However, there remains scope for differential application of the criteria to the two trial arms, so further strategies are needed.

Second, all ambulance clinicians in the trial will be trained in the trial procedures, to ensure that they understand the rationale for the trial and the importance of following the trial procedures correctly. The training will include a review of existing evidence so that participating ambulance clinicians understand the current position of equipoise regarding the effectiveness of LUCAS, and discussion of potential sources of bias in the trial and the importance of applying the inclusion/exclusion criteria rigorously to both arms. Training will continue throughout the recruitment period, to ensure that any new staff are trained before recruiting, and that important messages are continually reinforced.

Third, we will institute a programme of regular monitoring by analysing the characteristics of patients recruited to the LUCAS and manual compression arms and cardiac arrests where no resuscitation attempt was made, and the proportion of cardiac arrests recruited, to detect any imbalances that may be caused by different thresholds for resuscitation. We will also monitor the presenting rhythm, proportion of witnessed and un-witnessed arrests; presence of bystander CPR and time from 999 call to crew arrival (using ambulance computer log data). If a lower threshold for attempting resuscitation in the LUCAS arm exists we will find a greater number of recruits and a greater proportion of cardiac arrests with resuscitation attempts, a greater proportion with unfavourable presenting rhythms, a lower proportion of witnessed arrests and with bystander CPR, and longer times from 999 call to start of resuscitation in the LUCAS group. The frequency and mechanism of monitoring will be discussed with the Data Monitoring Committee.

If we suspect that a different threshold for resuscitation is being applied by any personnel recruiting to the trial, the first step will be to identify the personnel involved and ensure that their training in the trial procedures is up to date, and reinforce the essential messages about the rationale for the trial. The paramedic research fellows will develop close working relationships with the ambulance clinicians recruiting patients, and will be ideally placed to undertake this role.

Finally, we can, if necessary, correct for any inclusion bias in the statistical analysis of the trial, by adjustment of the analysis to take account of imbalance in factors such as presenting rhythm, time

since 999 call and presence of bystander CPR. We expect any potential inclusion bias to affect only the group of patients least likely to survive, and it would not affect patients for whom a resuscitation attempt would always be made (e.g. those with presenting rhythms with the highest probability of survival), and therefore a comparison between LUCAS and manual compression in the subgroups of patients in whom resuscitation is known to be appropriate would be unaffected.

Summary of monitoring

- 1) Proportion of arrests where resuscitation attempted: cardiac arrests attended
- 2) Age
- 3) % Bystander CPR
- 4) Time of 999 call to trial vehicle arrival
- 5) Proportion of patients in asystole

2.10.3 Monitoring device usage

Monitoring compliance (i.e. whether the device was used for all eligible patients in the LUCAS groups and none of the control group) will be achieved by monitoring the recordings taken by LUCAS-2 devices when in use. The devices automatically record data on date, time and duration of use, which will be downloaded and compared with reported usage of each LUCAS device to ascertain compliance. In addition we will request ECG recordings taken during resuscitation. These are recorded as part of the electronic data collection in Scotland. In Wales and the West Midlands data cards will be supplied by the trial and submitted with the report of each cardiac arrest. The data will be analysed by the trial co-ordinating centre to confirm whether LUCAS was used and to confirm the presenting rhythm and duration of resuscitation. Any discrepancies will be investigated and discussions about non-use or incorrect use held with the staff involved.

2.10.4 Learning effects

Because LUCAS will be a new device in the areas where we propose to run the trial, there is a possibility that there will be a learning effect, and its effectiveness may increase through time as personnel become more familiar with it and better at using it. We will therefore use a “run-in” period at each station before the start of recruitment to the trial. Participating vehicles will be randomised at the start of this period, LUCAS will be used in the LUCAS arm, and all trial data will be collected. This will enable staff to become familiar with the use of LUCAS in clinical practice and will enable us to test the trial procedures and data collection mechanisms. If there are no major problems, recruitment to the main trial will commence immediately at the end of the run-in period.

2.10.5 Crew preferences

With randomisation by vehicle, a potential source of bias is that ambulance clinicians who are motivated to use LUCAS will select LUCAS vehicles, and those who dislike LUCAS may avoid it. In order to check for this possibility, we will monitor crews attending cardiac arrests and investigate any suspicious patterns such as non-compliance with the allocated treatment or

possible selection of LUCAS or control vehicles. If found, the staff involved will be given extra training in the trial procedures.

2.10.6 Blinding

Because of the nature of the interventions, ambulance clinicians cannot be blinded, and will be aware of treatment allocations. Control room personnel will be blinded to the allocation of the ambulance service vehicles, to ensure that there is no bias in whether a LUCAS or control vehicle is sent to an incident that is likely to be a cardiac arrest. Normally the closest vehicle would be sent, which will give an equal chance that a LUCAS or control vehicle will attend. Patients themselves will be unaware of their treatment allocation at the time of the intervention, though they may subsequently be unblinded by relatives or friends who are aware that LUCAS was used. We will seek to ensure blinding of outcome assessment as far as possible. Mortality is an objective outcome, and its assessment will not be influenced by knowledge of the treatment allocation. Research nurses assessing outcomes at 3 month and 12 month follow-up will be blinded to treatment group and will endeavour to maintain their blinding during the follow-up assessments.

2.11 Trial Intervention / Treatments

2.11.1 LUCAS arm

The trial will use the LUCAS-2 device, the latest version of the LUCAS device, manufactured by Jolife AB, Ideon Science Park, Scheelevägen 17, SE-223 70 Lund, Sweden, and distributed by Physio-Control UK, Suite One, Sherbourne House, Croxley Business Park, Watford WD18 8WW.

The intervention arm will receive resuscitation according to the Resuscitation Council (UK)(37) and JRCALC Advanced Life Support Guidelines, with the exception that the LUCAS device will be deployed to replace standard manual chest compressions. All standard advanced life support interventions will be provided including drug administration, defibrillation and advanced airway management as required.

On arrival, LUCAS CPR will be administered whilst the defibrillator is set up, if the patient is in ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) a counter shock will be given. Operational experience shows that LUCAS can be deployed within 20-30 seconds of arrival at the patient. Prior to intubation, compressions will be provided using the 30 compressions : 2 ventilation mode. If the patient is intubated, asynchronous compressions and ventilations will be provided, with a ventilation rate of 10 per minute.

Defibrillation will be performed using the following sequence: stop LUCAS device, analyse heart rhythm; if shock indicated, restart LUCAS, charge, deliver shock, continue CPR for 2 minutes. This will minimize deleterious pre and post shock pauses in compressions. The LUCAS device will be used in place of standard chest compressions as long as continued resuscitation is indicated, including resuscitation in the field and during transport to hospital. The trial intervention will cease after care is handed over to the medical team in hospital or the patient is declared deceased according to the ROLE criteria.

2.11.2 Manual chest compression arm

The control arm will receive resuscitation according to Resuscitation Council (UK) and Joint Royal College Ambulance Liaison Committee (JRCALC) Advanced Life Support Guidelines. All

standard advanced life support interventions will be provided including drug administration, defibrillation and intubation as required.

On arrival, CPR will be administered whilst the defibrillator is set up, if the patient is in ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) a counter shock will be given. Before intubation, 30 manual chest compressions will be given followed by 2 ventilations. After intubation, asynchronous compressions and ventilations will be provided, with a ventilation rate of 10 minute.

Minimising interruptions in chest compressions are critical for optimizing the chances that a shock is successful. However, it is currently considered unsafe to perform defibrillation during manual chest compression. Defibrillation will therefore be performed using current UK recommendations, which are: stop CPR; analyse heart rhythm, re-start CPR whilst charging defibrillator, stop CPR, deliver shock, restart chest compressions and continue CPR for 2 minutes.

2.11.3 Post resuscitation care (both arms)

The care a patient receives in hospital following return of spontaneous circulation has a significant influence on final outcome. There is no reason to suppose that patients treated in the LUCAS as opposed to the manual compression arm would receive any different treatment in hospital.

If a patient in the LUCAS arm arrives at hospital with the LUCAS device running, the device should be removed and resuscitation should continue with manual compressions. Hospitals will be given information about the trial prior to the start of recruitment and will be encouraged to develop their own guidelines for continued use of LUCAS in the emergency department.

2.11.4 Guidelines 2010

The International Liaison Committee for Resuscitation and European Resuscitation Council (UK) published new resuscitation guidelines on 18th October 2010 which have been incorporated into this version of the protocol.

2.11.5 Training

All ambulance service personnel participating in the trial will require training in the use of LUCAS and in the trial procedures. A programme of face to face training will be provided at all participating stations before the start of recruitment, and regular ongoing training in LUCAS and the trial procedures as required, during the frequent visits that will be made to each station. In addition, training materials and information about the use of LUCAS and the study procedures will be made available via the trial website. This will include information about the operating parameters of the LUCAS device and where in the standard resuscitation algorithm it should be applied, and study inclusion and exclusion criteria, data collection and ethical and consent issues. The trial co-ordinating centre will maintain records of all personnel who have been trained in the use of LUCAS.

Training for ambulance personnel working within the catchment area of the study will be provided by paramedic research fellows employed by the trial. These are most likely to be ambulance staff seconded to the project on a part-time basis. To ensure continuity and ownership of the research, these personnel will also be responsible for monitoring recruitment at a local level and supporting recruitment among the ambulance service staff.

3. METHODS AND ASSESSMENTS

3.1 Data collection

3.1.1 Trial entry and outcomes up to hospital admission

Data will be recorded on all cardiac arrests. This will allow assessment of the proportion of cardiac arrests enrolled into the trial, and will help to ensure that no eligible cardiac arrests are missed. Data will be collected by the attending ambulance clinicians, using the routinely-completed Patient Report Form (PRF), which will be modified for the duration of the trial, if necessary, to include the required data. Data to be recorded will be:

- a. Vehicle and crew identifiers
- b. Date and time of arrival of vehicle at scene
- c. Whether trial vehicle was first resource on scene
- d. Whether resuscitation was attempted
- e. Whether patient known or believed to be ≥ 18 years old
- f. Aetiology of cardiac arrest (presumed cardiac/traumatic/submersion/etc)
- g. Location of cardiac arrest
- h. Whether patient known to be pregnant
- i. Date of birth
- j. Sex
- k. Whether LUCAS was used
 - i. If in LUCAS arm and not used, reason
- l. Outcome (ROSC at any time, whether transported to hospital, status at handover to hospital)
 - i. If resuscitation terminated on scene, time of termination
- m. If taken to hospital:
 - i. name of hospital
 - ii. time of arrival at hospital
- n. Time of 999 call
- o. Whether cardiac arrest was witnessed
 - i. If witnessed, by crew or bystander
- p. Whether there was bystander CPR
- q. Type of initial cardiac rhythm
- r. Patient's name or initials
- s. Patient's address
- t. Patient's telephone number

Items a to q will be collected for all eligible cardiac arrests. Items r to t will be required for all patients that are not known to have died before arrival at hospital, as these patients are potential survivors and may need to be contacted for follow-up. Data forms will be collected in a central place at participating ambulance stations and collected by research paramedics on a weekly basis. For ineligible cardiac arrests (no resuscitation attempt, < 18 years, pregnant, traumatic aetiology, non-trial vehicle was first on scene) the ambulance service will also send the trial co-ordinating centre details of the arrests for monitoring purposes (see section 2.10.2). If the patient did not survive to hospital, the

trial co-ordinating centre will be supplied with anonymised data (items a to q only); however date of birth will be included as this is required for the trial analysis.

3.1.2 Hospital

Hospitals will not undertake prospective data collection for trial participants, because of the logistical difficulties that this would present. Participants may be taken to any hospital in the trial regions; data collection from hospitals would therefore require the participation and training of a large number of clinicians, from several different departments within each hospital, who will have little engagement with the trial and no role in delivering the trial interventions. We will inform all hospitals in participating regions about the trial and ensure that they have information available for any clinicians or patients that need it.

3.1.3 Deaths

Deaths before admission to hospital will be recorded by ambulance services, and data for these patients will be supplied to the trial database in anonymised form, as no personal identifiers are needed for follow-up. Before transfer of data to the study co-ordinating centre, ambulance services will conduct their own checks of survival. These will differ between ambulance services, but will (where possible) include access to the NHS Personal Demographics Service.

To identify later deaths, all potential survivors will have their status checked with MRIS approximately six weeks after their cardiac arrest. This should allow the majority of deaths to have been included in the MRIS database. Deaths are normally included within four weeks of issue of a death certificate, and we anticipate that the majority of certificates will be issued within a few days. All survivors will be flagged on the MRIS database, to ensure that the study is notified immediately if their death is registered. Issue of a death certificate may be delayed in some cases by referral to a coroner, but in most cases the coroner's investigation will be concluded quickly and the delay to inclusion of the death on the MRIS database will be small.

3.1.4 Follow-up

Survivors will be followed up approximately 90 days after their cardiac arrest, by a home visit (or over the phone) from a study research nurse/paramedic. At this visit the quality of life measures (SF-12 and EQ-5D) will be completed, details of ICU and hospital discharge dates will be collected, and the nurse will make an assessment of CPC score.

The second follow-up visit at 12 months will include quality of life (SF-12 and EQ-5D), anxiety and depression (HADS), post-traumatic stress (PCL-C) and Mini-Mental State Examination (MMSE). The NHS Demographics Batch Service will be used to identify participants that have changed address since the last contact. Health service and social care resource use will be reported in a patient self completed questionnaire that will be provided to participants at 3 month and 12 month follow-up visits.

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse events (AE)

An Adverse Event (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 Serious Adverse Events (SAEs)

The definition of a Serious Adverse Event (from NRES(38)) is an untoward and unexpected occurrence that:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect (not relevant to this trial population).

4.1.3 Additional terms for device trials

For trials of devices, additional terms are used, defined as follows:

Adverse Device Effect/Event (ADE): Any unfavourable or unintended response to a medical device.

Serious Adverse Device Effect (SADE): An ADE that has resulted in any of the consequences of an SAE or might have led to those consequences if suitable action/intervention had not been taken.

Incident: Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which directly, or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to the serious deterioration in their state of health.

4.2 Events that should be reported

Serious Adverse Events and Serious Adverse Device Events should be reported to the Trial co-ordinating Centre on the appropriate form (found in the PARAMEDIC site file).

All of the patients in this trial will be in an immediately life-threatening situation, many will not survive, and all of those that do will be hospitalised. These situations are therefore expected, and events leading to any of them should only be reported as SAE/SADEs if their cause was clearly separate from the cardiac arrest. Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation (including death and hospitalisation) should not be reported.

Therefore, events should be reported as SAE/SADEs if they:

- are serious;
- AND are potentially related to trial participation i.e. may have resulted from study treatment such as use of the LUCAS device;

- AND are unexpected i.e. the event is not an expected occurrence for patients who have had a cardiac arrest.

Examples of events that may be SAE/SADEs are; use of LUCAS causing a new injury that endangers the patient, malfunction of the device causing injury to ambulance clinicians, malfunction of the device leading to inadequate chest compression.

4.3 Reporting SAEs

Events satisfying the criteria given above should be reported to the study co-ordinating centre as soon as they become apparent using the SAE/SADE Report form.

SAE/SADE reports received by the co-ordinating centre will be reviewed on receipt by the Chief Investigators and those that are considered to satisfy the criteria for being related to the device and unexpected will be notified to the main REC, MHRA and manufacturer within 15 days of receipt. SAE reports will also be reviewed by the DMC at their regular meetings, or more frequently if requested by the DMC Chair.

Adverse events that are not considered to be serious will be logged and included in annual progress reports.

4.4 End of the Trial

The trial will end when the 12 month follow-up of the last patient is closed (i.e. when the follow-up is completed or the patient is classified as lost to follow-up).

The trial will be stopped prematurely if:

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

The Research Ethics Committees will be notified in writing if the trial has been concluded or terminated early.

5. DATA MANAGEMENT

The flow of information between the Ambulance Services and the Co-ordinating centre is summarised in the Information Flow Diagram (Appendix 1).

All data collected during the trial will be handled and stored in accordance with the Data Protection Act 1998. Data will, as far as possible, be anonymised, but this trial will involve the use of identifiable personal data for follow-up. All transfer of data between ambulance services and the Study Co-ordinating Centre will use secure methods such as encrypted email.

Data from ambulance services will be forwarded to the trial in anonymised format (identified by study number) for patients known to have died prior to follow-up. For survivors, who are eligible for follow-up, identifying information will be passed to the co-ordinating centre as discussed in section 2.7.

Follow-up data will be collected by research nurses during home visits. Data will be entered into the study database at the Co-ordinating centre.

5.1 Database

All study data will be entered into a study-specific database that will be set up by the Programming Team at WCTU at the start of the study. All specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer, statistician, chief investigators and trial co-ordinator.

5.2 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. 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 study. All databases containing identifiable information will be password protected. Any data that are transferred out of the secure environment (for example for statistical analysis) will be anonymised and individual participants identified by study number only.

5.3 Monitoring

Trial staff or paramedics will select 10% of records to monitor at the end of each recruitment year. Records will be retrieved from the Ambulance Trust Audit team and checked against the data held in the trial database.

5.4 Archiving

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

6. ANALYSIS

6.1 Statistical analysis

All analyses will be by intention to treat, and all estimates will be adjusted to account for the cluster randomised design. Dichotomous outcomes (survival to 30 days, hospital discharge, 3 months and 12 months, and neurologically intact survival) will be presented as risk ratios and 95% confidence intervals. Survival time and other time to event outcomes (duration of hospital and ICU stay) will be analysed using survival analysis, with adjustment for clustering and important covariates, with results presented as hazard ratios and their 95% confidence intervals. Continuous outcomes (quality of life, anxiety and depression, cognition and post traumatic stress) will be analysed by multi-level linear regression, with adjustments for clustering and important covariates. The results will be presented as the difference in means between the groups and its 95% confidence interval. CPC score will be analysed by multi-level ordinal logistic regression(39) and the results will be presented using odds ratios and their 95% confidence intervals. Reporting of analyses will follow CONSORT guidelines for the reporting of cluster randomised trials.(40) A detailed analysis plan will be drawn up by the study statisticians and approved by the DMC.

Four pre-specified subgroup analyses will be conducted:

1. cardiac arrest witnessed by crew; witnessed by public; versus not witnessed;
2. bystander CPR versus no bystander CPR;
3. type of initial rhythm (VF/VT; PEA; asystole);
4. presumed cardiac aetiology of cardiac arrest (to conform with Utstein recommendations).

All subgroup analyses will use statistical tests of interaction.(41)

In addition, we will model the effects of age and the time interval from 999 call to arrival of the trial vehicle on the effects of the LUCAS intervention, using regression analyses. These subgrouping variables will not be categorised or dichotomised, as there is no clear biological rationale for any particular cut-points, and there is good evidence that any form of categorisation of continuous variables is potentially misleading.(42, 43) We will explore non-linear relationships between the covariates and outcome, using the multivariable fractional polynomial interaction (MFPI) technique(44) and the STEPP procedure (Subpopulation Treatment Effect Pattern Plot).(45)

Interim analyses will be conducted at least once per year during recruitment and supplied confidentially to the DMC. The DMC will consider the results of the interim analysis and make recommendations to the Trial Steering Committee about continuation of recruitment or any modification to the trial that may be necessary. The data collected during the three-month run-in period will be supplied to the DMC for the first interim analysis. They will also be included in the final report, but reported separately from the results of the main recruitment period.

6.2 Economic analysis

The economic evaluation will consist of two distinct but complementary sets of analyses. The first analysis will be a within-trial cost effectiveness analysis, which will have the same time horizon as the trial and compare the observed costs and outcomes of the intervention and control patients from recruitment to the end of trial follow-up. The second analysis will adopt a lifetime horizon and will estimate the long-term incremental cost effectiveness of the LUCAS by constructing a decision analytic cost effectiveness model. A lifetime horizon is necessary to produce an unbiased estimate of incremental benefit whenever there is a potential difference in the mortality between the comparators.

For the within trial economic evaluation the interventions (LUCAS vs. manual compression) will be compared in terms of the Quality Adjusted Life Years (QALYs). The utility weights for calculating the QALYs will be derived from the SF-12 data (46) via the SF-6D algorithm.(47) The primary analysis will adopt the perspective of the UK NHS and Personal Social Services (NHSS&PSS). Consistent with this perspective we will identify, quantify and value resource utilisation within these budgets. As far as possible unit costs will be obtained from national routine datasets such as the NHS Reference cost index, British National Formulary and the PSSRU Costs of Health and Social Care. Health and social care resource use will be obtained from the trial case report forms and simple self complete questionnaires. Where appropriate the costs and outcomes will be discounted at 3.5% per annum, according to current recommendations.(48) We will estimate the uncertainty around the mean costs and outcomes in each group using the non-parametric bootstrap. The outcomes will be reported as the expected incremental cost effectiveness of LUCAS-2 compared to usual care; the Cost Effectiveness Acceptability Curve and the expected net benefit assuming lambda takes a value of £15K, £20K and £25K.

A micro-costing study will be undertaken to establish the unit cost for the LUCAS device. This will include the cost purchase, initial and on-going staff training and maintenance. The frequency of use

observed in the trial will be used to estimate the expected number of applications in order to calculate the expected cost per application.

The long term cost effectiveness analysis will adopt the same perspective as the within trial analysis. The outcome measure will also be the QALY and the approach to costing care will be the same. In line with best practice, the structure of the decision analytic model will be developing collaboration with the clinicians involved in the trial. Workshops will be held to obtain a consensus on the typical clinical pathway for survivors of cardiac arrest post discharge from hospital. Health and social service interventions associated with sub-pathway will be identified. The costs and expected outcomes of these interventions will be estimated using national cost databases and syntheses of the published evidence respectively. Costs and outcomes will be discounted at 3.5% per annum. The uncertainty in the estimated mean costs and effects will be quantified using probabilistic sensitivity analysis, which will be operationalised using Monte Carlo simulation analyses. The outcomes will be reported as the expected incremental cost effectiveness of LUCAS compared to usual care; the Cost Effectiveness Acceptability Curve and the expected net benefit assuming lambda takes a value of £15K, £20K and £25K.

If there is large uncertainty regarding the expected cost effectiveness of introducing the LUCAS we will undertake value of information analyses to identify the key drivers of the uncertainty, assess whether it is worth undertaking further research and if so, what specific pieces of research would be of the greatest value to UK NHS decision makers.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Ethical conduct of the trial

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with MRC Good Clinical Practice and applicable regulatory requirements.

The trial will be subject to the requirements of the Mental Capacity Act 2005 in England and Wales and the Adults with Incapacity (Scotland) Act 2000, and has approval from the Scotland A Research Ethics Committee and the Coventry Research Ethics Committee in England and Wales. R&D departments of participating NHS Trusts have also given approval. Approval has been given by the National Information Governance Board for Health and Social Care Ethics and Confidentiality Committee for access to personal data without consent (ref: ECC 2-02 (c)/2011).

7.2 Sponsor

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

7.3 Relationship with manufacturer of LUCAS

The manufacturers (Jolife AB) and distributors (Physio-Control UK) of the LUCAS device will have no role in the design, conduct, analysis or reporting of the trial. Their role will be limited to supply and servicing of LUCAS devices, and training of study co-ordinating centre personnel.

7.4 Indemnity

Staff employed by the NHS will be covered by the Clinical Negligence Scheme for NHS Trusts. Staff employed by the University of Warwick will be covered by the University's trial insurance. Negligent harm cover will be provided by standard NHS arrangements (HSGG(96)48). 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.

7.5 Administration

The trial co-ordination will be based at Warwick Clinical Trials Unit, University of Warwick.

7.6 Trial Management Group (TMG)

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

7.7 Investigators Group

The Investigators team will meet regularly throughout the trial, either face to face, by teleconference or through other means of communication

7.8 Trial Steering Committee (TSC)

A Trial Steering Committee, 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 study 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

The membership of the TSC is: Prof Jon Nicholl (University of Sheffield; Chair), Prof Helen Snooks (Swansea University), Dr Alasdair Gray (Emergency Medicine, Royal Infirmary of Edinburgh), Dr Fiona Moore (London Ambulance Service), Mr John Long (Royal Life Saving Society), Fr Neil Baylis (lay member), Martyn Box (South West Ambulance Service), Dr Simon Gates (investigator), Dr Gavin Perkins (investigator), Prof Malcolm Woollard (investigator).

7.9 Data Monitoring Committee (DMC)

The Data Monitoring Committee 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 Trial Steering Committee 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.

The membership of the DMC is: Prof Marion Campbell (University of Aberdeen; Chair), Prof Kathy Rowan (ICNARC), Dr Jerry Nolan (Royal United Hospital). DMC meetings will also be attended by the Chief Investigators (for non-confidential parts of the meeting) and the trial statistician.

7.10 Essential Documentation

A Trial Master file will be set up and held securely at the co-ordinating centre.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

8.1 Compliance

See also Section 2.10.3. Use of LUCAS will be verified in two ways; by ECG recordings taken by ambulance clinicians during resuscitation and supplied as hard copies, and by analysis of data on time and duration of use collected by the LUCAS-2 devices. These data will be downloaded periodically, and will be compared against records of use of the LUCAS devices during resuscitations.

8.2 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.

8.3 Differential recruitment

We will monitor the characteristics of patients recruited to the two trial arms (presenting rhythm, proportion of witnessed and un-witnessed arrests; presence of bystander CPR, time from collapse to crew arrival, and time from 999 call to crew arrival) and also for those attended by a non trial vehicle and where no resuscitation attempt was made, to detect any imbalances that may be caused by different thresholds for resuscitation. See also Section 2.10.2. Analyses will be performed by the trial statistician on a regular basis, at least once per month.

8.4 Training

All ambulance clinicians participating in the trial will be trained in the use of LUCAS, and records will be kept of attendance at training sessions.

9. 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 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.⁽⁴⁰⁾ 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.

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 Procedure 22 (Publication and Dissemination).

10. FINANCIAL SUPPORT

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APPENDIX 1: Flow chart for identifying participants and checking death

