Appendix 8: Statistical Analysis Plan

Pre-hospital Randomised Assessment of a

Mechanical Compression Device in Cardiac Arrest

STATISTICAL ANALYSIS PLAN

FOR THE PARAMEDIC TRIAL

Authors: PARAMEDIC Trial Team

Completion date:

Approved by:

CONTENT **Page**

SECTION 1: AIMS AND DESIGN OF THE TRIAL

1.1 Trial design

PARAMEDIC is a cluster randomised controlled trial in the UK ambulance services. The vehicle (ambulances and rapid response vehicles (RRVs)) will be the units of randomisation.

1.2 Objectives

1.2.1 Primary objective

The primary objective of this trial is to evaluate the effect of using LUCAS rather than manual chest compression during resuscitation of a patient by paramedics after out of hospital cardiac arrest on mortality at 30 days after event.

1.2.2 Secondary objectives

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.

1.3 Eligibility criteria

1.3.1 Eligibility for clusters

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.

1.3.2 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

1.4 Outcome measures

1.4.1 Primary outcome:

Survival to 30 days post cardiac arrest.

1.4.2 Secondary outcomes:

- Survived event (sustained return of spontaneous circulation (ROSC), with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital)
- Survival to hospital discharge
- Hospital length of stage
- Intensive care length of stay
- Survival to 3 and 12 months
- Health related quality of life (SF12 and EQ-5D) – 3 and 12 months
- Neurologically intact survival (survival with CPC score 1 or 2)- 3 months only
- Cognitive outcome months (Mini Mental State Examination (MMSE))- 12 months only
- Anxiety and depression (Hospital Anxiety and Depression Scale (HADS)) – 12

months only

- Post Traumatic Stress (PTSD civilian checklist (PCL-C)) – 12 months only

An economic evaluation will also be conducted, and is described in a separate analysis plan.

1.4.3 Safety

Adverse events and device related adverse event will be reported.

SECTION 2: MONITORING OF THE TRIAL

Monitoring of the trial is a continual process, from the start to the end of the study. At the end of the trial two aspects related to monitoring will be examined:

(a) Operational (logistical) and Process Management monitoring;

(b) Statistical monitoring (assessment of bias – as stated in the protocol).

2.1 Operational (logistical) and Trial Management of Ambulance Stations

- There are 4 *regions* recruiting patients to the PARAMEDIC trial: West Midlands, Wales, North East and South Central.
- Within the regions are the local areas (*locality*) and within the localities are the *ambulance stations*, where vehicles have been randomised to the trial.
- The status of the recruiting ambulance stations will be detailed (as in Table 1.1).

2.2 Operational (logistical) and Trial Management monitoring of vehicles

2.2.1 *Number of vehicles and its impact on the Sample Size*

- The observed number against what was expected for the number of vehicles will be stated and its effect on the overall sample and intra cluster correlation coefficient.

2.2.2 *Vehicle Movement and Rotation*

- There are many processes in the PARAMEDIC trial that need to be monitored regularly and at the end of the trial -in order to make the trial a success. This will highlight any areas which have been problematic and may have introduced bias.

(a) Not all vehicles are randomised in a station. Non-randomised vehicles may attend cardiac arrests. The number of non-randomised vehicles will be summarised as a proportion of all vehicles in a station/area.

(b) Some vehicles are likely to be randomised in a region and can sometimes be moved to another region, end up in workshop (trial or non-trial) or scrapped.

(c) Some vehicles are randomised but never attend a cardiac arrest, and this means that the randomised devices are held up and never get used. Also for the sample calculation purposes, we have assumed that on average each randomised vehicle will attend at least 15 cardiac arrests.

The above will mean that randomised vehicles are less likely to attend cardiac arrests, in the presence of non-trial vehicles and it is important to ensure that randomised vehicles keep within their region when rotation occurs.

Summary of vehicle movement and rotation

1. Number of vehicles (randomised and non-randomised) within each vehicle type and each region (TABLE 2.1).

2. Number (and percentage) of vehicles RANDOMISED by the type of vehicle and intervention within each region - (TABLE 2.2) and FIGURE 2.1 (CONSORT Diagram).

4. Number (and percentage) of CURRENT vehicles by the type of vehicle and intervention within each region (after removal/change in allocation/change to another region) (TABLE 2.3 and TABLE 2.4).

6. Randomised vehicles attending number of cardiac arrests (TABLE 2.5 and TABLE 2.6).

2.3 Operational (logistical) and Trial Management monitoring of patients

2.3.1 Recruitment of patients

- Patients recruited within region/locality are detailed in Table 1.1.
- The average number of patients within each vehicle will be detailed.
- A recruitment graph showing the number of vehicles (control and LUCAS) recruited with the number of patients recruited over the entire study period will be illustrated (PLOT 1.1).

2.3.2 Distribution of patients within each region

- TABLE 3.1 through to TABLE 3.4 illustrate the distribution of patients within regions.

2.3.3 Violations or deviation from the protocol

- Protocol violators/deviators will fall into one of the following categories (tabulated in Table 3.3):

(i) Patients who receive an intervention different from that allocated to first vehicle in attendance;
(ii) Withdrawals;
(iii) Ineligible patients – any patient who was ineligible but subsequently received treatment from one of the randomised vehicles (and interventions).

- Withdrawals from the trial may occur during follow-up. All withdrawals will be summarised by treatment arm. Also all data up to the time of withdrawal will be used for the analysis (ITT).

2.3.4 Non-compliance

- Those in category (i) above make up the non-compliance group. These are further broken down into those listed in Table 3.5.

- The reasons for non-compliance as given in Table 3.5, can be split into two main groups:

(i) Trial specific non-uses of LUCAS: There are other reasons for non-use of LUCAS which are trial specific, and would not occur if the device should have in clinical practice. These include (a) crews not trained in use of the device, (b) crew error (protocol confusion or no device in vehicle or crew forgot or the device having been removed erroneously from the vehicle).

(ii) As encountered in normal clinical practice: These include (a) unsuitable patient (patient was too big or too small), (b) device issues (device failure), (c) not possible to use LUCAS (either because of space restrictions, or because the cardiac arrest occurred after attendance of a solo responder who did not take the LUCAS to the patient). Such cases are part of the real-world treatment effect of LUCAS and are appropriately included in analysis of a pragmatic trial.

- These two groups are included in the sensitivity analysis for this study (see section 5.2.4).
- At the beginning of the trial, the rate of non-compliance is considered as 100%, and as each non-compliant patient enters the trial through time, the rate of non-compliance will decrease. This rate can be plotted against days of survival on a Kaplan-Meier curve for those on the LUCAS arm. This will allow us to assess the relationship of survival with the rate of non-compliance.

2.3.5 Status of patients in the trial from prior to hospitalisation to follow-up

TABLE 3.5 illustrates the status of patients in the trial, at the end of the study.

2.3.6 Follow-up rates

The follow-up rates will be derived from information presented in Table 3.5.

2.3.6 *Safety Data*

Device related events and serious adverse events will be summarised in a listing (by intervention.

SECTION 3: STATISTICAL MONITORING

3.1 Statistical monitoring (assessment of bias)

- Ambulance crew who deliver the interventions are not blinded to the allocation, and therefore there is a possibility that bias could be introduced by different thresholds for resuscitation between LUCAS and the standard care arms. Appendix 1 details the staff involved in the trial and whether they are blinded/un-blinded to the treatment allocation.

- Table 4.1 illustrates the variables which will be assessed to detect any bias introduced into the trial: assessment of characteristics of patients recruited to the LUCAS and manual compression arms, where cardiac arrests occurred and no resuscitation/ resuscitation was made.

- The data on the characteristics of patients (for assessment of bias) is reported to the DMC on a 3 monthly basis. The DMC assesses these for any variables that may exceed potential thresholds (as judged by the clinical experts). Table 4.1 will also be produced at the end of the trial.

- In addition the following will be summarised for monitoring purposes:

  - Proportion of arrests where resuscitation attempted: cardiac arrests attended;
  - Age (summary statistics);
  - % bystander CPR;
  - Time of 999 call to trial vehicle arrival;
  - Proportion of patients in asystole.

3.2 Intra cluster correlation coefficient and sample size

- Several patients are likely to be attended by one vehicle. In theory this gives arise to the fact that there is a grouping component (by the vehicle) which may indicate that outcome is correlated among patients who have been attended by a particular vehicle. However, in practice, all vehicles are mechanical objects and there are no subjective factors which distinguish them. Furthermore, different personnel and rotation of staff would means that the different paramedics are likely to attend cardiac arrest, using one vehicle, at least some of the time, suggesting that any clustering effects will be negligible.

- However the intra cluster correlation coefficient will be obtained using the primary outcome.
- The intra cluster correlation coefficient will be computed for every DMC report and its impact will be assessed on the sample size.

- Event (survival status) at 30 days is the primary outcome and can be interpreted as binary (death/alive) at that time point. Chakroborty (Contemporary Clinical Trials 30 (2009) 71–80) specify the formulation of an ICC based on binary outcome together with the 95% confidence interval. This will be used in computing the ICC estimate.

3.3 Sample size and non-compliance

To ensure the required sample size is achieved, we will monitor non-compliance and its impact on the sample size/effect size that is required.

SECTION 4: STATISTICAL ASPECTS

4.1 Outcome Variables

OUTCOMES	TIME POINT	SCORING
Primary outcome		
Survival	30 days post cardiac arrest	
Secondary outcomes		
Survival event (sustained return of spontaneous circulation (ROSC))	Until admission and transfer of care to medical staff at the receiving hospital	
Survival to hospital discharge	The point at which the patient is discharged from the hospital acute care unit regardless of	

	neurological status	
Survival	To 3 months and to 12 months	
Health related quality of life-SF-12	At 3 months and at 12 months	As in the SF-12 manual: How to Score version 2 of the SF-12 Health Survey. Two provided : Physical and mental components.
Health related quality of life- EQ-5D	At 3 months and at 12 months	Summary of each item given and the VAS score (out of 100) summarised. The EQ-5D utility score will be obtained by the Health Economist.
Neurological intact survival (survival with CPC score 1 or 2)	To 3 months	The CPC score is measured on a 5-point scale. However, it is generally acceptable to split these into two categories: good neurological outcome (CPC score: 1-2) and poor neurological outcome (3-5).
Cognitive outcome (Mental Mini State Examination)	At 12 months	Each item scores a 1 if it is correct or 0 if incorrect. The total score is summated and the maximum score is 30. Cut-off are: 0-10: severe, 10-20: moderate, 20-25: mild, 25-30: questionably significant.
Anxiety and depression score (Hospital Anxiety and depression scale)	At 12 months	There are 14 items: 7 relate to anxiety and 7 relate to depression. Responses are summed to provide separate scores for anxiety and depression, with possible scores ranging from 0 to 21 for each scale

		Higher scores indicate likelihood of anxiety and/or depression. Recommended cut-off are : 8-10 (mild); 11-15(moderate) and 16 or above (severe)
Post Traumatic stress (PTSD civilian checklist (PCL-C))	At 12 months	Respondents rate each item from 1 ('not at all') to 5 ('extremely') to indicate the degree of the symptoms over the past month. Thus the total will range from 17 to 85. Weathers et al (1993) recommended a cut-off score of 50 as optimal for indicating a probable of combat-related PTSD.
Hospital length of stay	Up to hospital discharge	
Intensive care length of stay	Up to ICU discharge	

4.2 Type of populations

4.2.1 Intention to treat (ITT) Population

An ITT analysis would measure something more important than intervention efficacy, namely intervention policy. That is, it tests whether it is better to *prescribe* LUCAS than manual CPR (i.e. an 'as-randomised analysis' or intention to treat (ITT) compares the outcomes of participants by assigned group). The ITT effect is the effect of treatment assignment rather than the effect of treatment taken (often called 'effectiveness' as opposed to 'efficacy'). A full 'Intention-to-treat' analysis is only possible when complete outcome data are available for all patients. One of the main reasons for advocating ITT analysis is that it gives an estimate as would be in the 'real world' and it also maintains the baseline comparability achieved by the randomisation process. If the initial random assignment is undermined, then confounding can be introduced and the internal validity of the results is consequently questionable.

4.2.2 Complier average causal effect (CACE)

The 'Complier average causal effect' (CACE) is the intervention effect among the true compliers; the difference in outcome between compliers in the treatment group and those controls who would have complied with intervention had they been randomised to the treatment group. Complier average causal effect (CACE) is a measure of the causal effect of the intervention on the patients who receive it as intended by the original group allocation. Because it retains the randomisation assignment, it overcomes the problems related to per-protocol and on-treatment analysis.

CACE analysis makes two assumptions; the first is that members of the control group have the same probability of non-compliance as members of the intervention arm. If allocation is genuinely random, this statement must be accepted as true. This second is that merely being allocated to the intervention has no effect on outcome; i.e. outcomes are the same for participants who were not treated with LUCAS in both the LUCAS and control arms. Both of these assumptions appear reasonable for this trial.

4.2.3 Proposed analysis strategy

In section 2.3.4, reasons of non-compliance were divided into two groups: those that were 'true non-compliers' and those which in a pragmatic setting could be considered as compliers.

In terms of analyses, we propose to use the following to estimate the effects of LUCAS. There will be two primary analyses.

PRIMARY ANALYSES:

(i) *Intention to treat analysis (PRIMARY):* This will include all patients recruited to the study.

(ii) *Modified CACE analysis (PRIMARY):* In this analysis, 'non-compliers' in the LUCAS arm will be defined as cases where non-compliance was due to: (a) crew not trained in use of the device, (b) crew error (protocol confusion or crew forgot) or (c) no device in the vehicle (the device having been removed erroneously).

SECONDARY ANALYSES:

(iii) *CACE analysis*: In this analysis all 'non-compliers' will be defined as 'all cases that did not receive their allocated intervention' i.e. LUCAS was not used if allocated to LUCAS, or LUCAS was used if allocated to control.

4.3 Analysis Datasets

Usually there are two datasets used for the statistical analysis (within each of the analyses populations stated in section 5): (a) Observed and (b) imputed.

For the primary outcome and data collected prior to hospital discharge only the observed datasets will be used for the ITT and 'CACE' analysis. This is because we cannot assume 'randomness' about the 'missing' data for these outcomes (i.e. death may be more associated with patients who have poor prognosis as will cardiac arrest outcomes).

However, follow-up data on questionnaires (SF-12 and EQ-5D) will be imputed for completeness.

4.3.1 Observed dataset

This will comprise of all the data observed (including follow-up) with missing values. The data will also include a variable to indicate what treatment patients were randomised to and another variable to indicate what treatment they actually received so that the 'ITT' and 'CACE' analyses can be implemented.

4.3.2 Imputed dataset

Data will also be imputed to form a dataset to be used for a sensitivity analysis for the follow-up questionnaires.

Data can be missing in fields in two situations: (a) when it is not applicable (validly missing) and (b) it can be missing due to patient/health professional leaving fields blank when they should have completed the question with an answer (invalidly missing). The latter will be examined for the different data mechanisms (MAR - missing at random; NMAR - not missing at random; MCAR - missing completely at random) and we will assess whether multiple imputation is viable. In the case where multiple imputation can be used and the data can be assumed normal, multivariate methods will be applied. In the case where one cannot assume a distribution of the data, the ICE (imputation by chain equations) will be used.

SECTION 5: MAIN STATISTICAL ANALYSIS

5.1 Demography of patients and Cardiac arrest population

Table 4.1 illustrates the patient characteristics of all patients approached and those who are eligible.

Table 4.2 displays the patient characteristics of eligible patients by intervention arm.

The tables illustrate the statistics for the compliers and non-compliers. No statistical analysis will be done for these tables.

5.2 Outcome Data

Unadjusted and adjusted estimates of the treatment effect will be obtained, with the 95% confidence intervals.

The analysis will be adjusted to take account of imbalance in factors (such as presenting rhythm, time since 999 call and presence of bystander CPR. Other factors which will be adjusted for will be age and gender.

The statistical analysis will be carried out using SAS (version 9.3.1) and STATA 11.

5.3 Primary outcome data

The primary outcome will be summarised as in Table 6.3. There is very little data where the outcome at 30 days is not known. For this reason, the data will be treated as a dichotomous without any censoring. The analysis will be carried out an intention to treat basis, as well as CACE and modified CACE.

ITT analysis

Assuming clustering effects: If there is noticeable clustering effect (as assessed with the intra cluster correlation coefficient), among the vehicles then this will need to be accounted for in the analysis. This will be done in SAS using GLIMMIX, where the vehicle (unit of randomisation) will be included as a random effect. Section 3.2 details the methods for assessing an ICC, which will quantify the clustering effect.

Assuming no clustering effect: Logistic regression models will be used to model the status of survival at day 30 (dead/alive), accounting for covariates such as age and gender.

Modified CACE and CACE data

Assuming clustering effects: For the modified CACE and CACE analysis, random effect model computing the Nagelkerke's estimate (1) will be used.

Assuming no clustering effects: For the modified CACE and CACE analyses, logistic regression models which are modified to allow for compliance/non-compliance effect will be used (based on the Nagelkerke's estimate (1)).

5.4 Secondary outcomes – up to hospital discharge

Tables 4.5 and 4.6 display the variables collected up to the point of hospital entry.

5.4.1 Sustained return of spontaneous circulation (ROSC)

ROSC will be summarised by each treatment arm (as in Table 4.6a) and summarised by each treatment arm and the type of compliance/non-compliance (Tables 4.6b and 4.6c).

Intention to treat: ROSC will be analysed using random effect logistic regression model (if clustering is present) or ordinary logistic regression model (if no clustering effect is present).

Modified CACE and CACE analysis: ROSC will be analysed using logistic regression models which are modified to allow for compliance/non-compliance effect (based on the Nagelkerke's estimate (as above)).

5.4.2 Survival to hospital discharge

Intention to treat: Table 4.7a summarises the summary statistics for survival to hospital discharge. The number of patients surviving/died at hospital discharge will be summarised and analysed using random effect logistic regression models (where there is clustering) or the usual logistic regression model (where there is negligible clustering).

Time to hospital discharge will be analysed using survival methods. In particular survival analysis which allows for random effect (namely frailty models) will allow for

the clustering component. In the case where there is very little clustering effect, the usual survival analysis (Cox's proportional hazards model) will be used.

Modified CACE and CACE: Table 4.7b and 4.7c illustrate the summary statistics for survival to hospital discharge, by intervention and by compliance/non-compliance. The above methods (as for the primary outcome) will be used allowing for compliance/non-compliance.

5.4.3 Length of intensive care and hospital stay

Intention to treat: Table 4.8a illustrates the length of intensive care and hospital stay. The length of intensive care and hospital stay will be summarised using mean, standard deviation and median values. These data will be analysed using random effect models (to account for clustering) or the using linear regression model (where the clustering effect is negligible).
Modified CACE and CACE: Table 4.8b and 4.8c illustrate the summary statistics for length of stay of intensive care and hospital stay, by intervention and by compliance/non-compliance. The above methods (as for the primary outcome) will be used allowing for compliance/non-compliance. These methods can be adapted for linear regression models.

5.5 Secondary outcomes – during follow-up

5.5.1 Survival to 3 and 12 months

Tables 4.9 (a, b and c) and 4.10 (a, b and c) illustrate survival status at 3 and 12 months.

Survival to 3 and 12 months (post cardiac arrest) will be assessed in a similar way as survival to 30 days (post randomisation).

5.5.2 Health related quality of life – SF -12 (3 and 12 months)

The health related quality of life SF-12 assessments (physical and mental components)will be summarised by intervention (as in Tables 4.11a, 4.11b and 4.11c) for 3 and 12 months.

The analysis of the SF-12 components will be similar to that for the length of stay (in ICU and hospital) as stated above, at each time-point.

5.5.3 Health related quality of life – SF -12 (3 and 12 months)

The health related quality of life EQ-5D assessments will be summarised by intervention (as in Tables 4.12a, 4.12b and 4.12c) for 3 and 12 months.

There will be no analysis for the items, however the VAS EQ-5D score will be analysed in a similar way to length of stay (in ICU and hospital) as stated above, at each time-point.

5.5.4 CPC scores(neurological intact survival) 3 months

The CPC scores will be summarised over the two interventions at 3 months, as given in Tables 4.13 (a, b and c).

The analysis of these scores will be using ordinal regression models.

5.5.5 Cognitive outcome (MMSE)

The cognitive outcome (MMSE) at 12 months will be summarised as displayed in Tables 4.14 (a, b, and c).

The analysis of the MMSE will be similar to that stated above for length of stay (in ICU and hospital stay).

5.5.6 Hospital Anxiety and Depression score (HADS)

The Hospital Anxiety and Depression score (HADS) at 12 months will be summarised as displayed in Tables 4.14 (a, b, and c).

The analysis of the HADS will be similar to that stated above for length of stay (in ICU and hospital stay).

5.5.7 Post Traumatic Stress (PTSD civilian checklist (PCL-C))

The Post Traumatic Stress (PTSD checklist) at 12 months will be summarised as displayed in Tables 4.14 (a, b, and c).

The analysis of the PTSD checklist will be similar to that stated above for length of stay (in ICU and hospital stay).

5.6 Sub-group Analyses

Six pre-specified sub-group analyses will be conducted:

- Cardiac arrest witnessed by crew/witnessed by public versus not witnessed;
- Bystander CPR versus no bystander CPR;
- Type of initial rhythm (VT/VF versus PEA/Asystole);
- Presumed cardiac aetiology of cardiac arrest (CPC score 1,2 versus 3,4,5)
- Type of vehicle (ambulance versus RRV)
- Ambulance service

These sub-group analyses will be conducted on the ITT (detailed in Tables 4.15-4.19). They will involve modelling the primary outcome as the independent variable and interaction of treatment and covariate of interest. Thus the modelling will be based on logistic regression and will be analysed in a similar way to the primary outcome (depending on whether clustering is present or not).

Further sub-group analyses will involve:

- Age
- Time interval from 999 call to arrival of the trial vehicle

These variables will be treated as continuous and therefore multivariable polynomial interaction (MPFI) technique will be used to assess the effect of treatment and covariate interaction.

SECTION 6: ADDITIONAL STATISTICAL ANALYSIS

6.1 Training of Paramedics/Learning Effects/Crew Preference

All clinician staff will be treated 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 members are trained before recruiting and that important messages are continually reinforced.

1. *Training of the Paramedics:* The percentage of crew trained (of all those trained to date at one round of training), the percentage of LUCAS uses (of all CAs attended by CPR and LUCAS) and the percentage survival (on LUCAS) will be plotted over the course of the study, i.e. by 3 monthly intervals (PLOT 2.1). This will illustrate a relationship between the increase in training, and use of LUCAS and its impact on survival. This plot will be done over the entire trial (i.e. time-points) and by localities.

2. *For compliance and non-compliance (separately):* The number of days from training to first use of LUCAS will be plotted against the percentage of LUCAS use for each paramedic. This will illustrate whether there is a relationship between lapse in time from training and the how often paramedics use the LUCAS device (PLOT 2.2).

3. *Learning effects:* A paramedic may have been trained to use the LUCAS device, but because he is part of a team, he may have not used it on a patient or his use of the device will be limited. Also, we only know of a team attending a cardiac arrest and its outcome, we do not know which paramedic administered the device. For this reason it would not be possible to look at learning effects within a paramedic. Also, team members that form teams differ all the time and again it would not be possible to look at the learning effects within teams. However, PLOT 2.1 above will inform us to some extent about the increase in the use of LUCAS over time and its effect on survival. Although this is does not measure learning effects directly, it does provide some information about whether the

outcome is getting better when the familiarity with the LUCAS device has increased across the trial.

4. *Crew preference:* the date of training will be plotted against the number of LUCAS uses for each paramedic (PLOT 2.3). One would expect to see a negative relationship: the earlier the date of training the more incidences a paramedic will have attended where the LUCAS was used. Any outliers, e.g. the later trained crew members who show a large number of incidences of cardiac arrests where LUCAS was used, may be valid, but will be investigated to eliminate any suspicious of crew preference.

The number of times a particular paramedic is present in a non-compliance case when using LUCAS will be summarised. Those who show a high incidence will be investigated. This will illustrate the presence of the paramedic when the LUCAS was not used according to the protocol. It will not directly indicate that the paramedic had lack of preference to the LUCAS device.

6.2 Monitoring Device Usage

Quality of CPR (via manikins, via defibrillators and all devices)

- The data collected on the manikins (ventilation: average volume, average per min; average depth: average per minute) will be used to compute the chest compression fraction.

- The quality of CPR via defibrillators will be assessed using the chest compression fraction obtained from the data on these devices (namely , time switched on to 1st compression, time from 1st compression to last compression, total time in pause, duration in 30:2, duration in continuous).
- Data obtained from all devices will lead to the computation of the chest compression fraction.

For each of these methods, the chest compression fraction will be summarised and where required cross referenced.

REFERENCE

N. Nagelkerke, V. Fidler, R. Bernsen, M. Borgdorff, Estimating treatment effects in randomized clinical trials in the presence of non-compliance, Statistics in Medicine, 2000, 19: 1849-1864

APPENDICES

APPENDIX 1

PARAMEDIC trial - Allocation concealment and blinding

In the PARAMEDIC study, failure to conceal the process of random allocation will potentially result in a non-randomised trial, while successful allocation concealment will reduce selection bias. Currently the method of randomisation is randomly allocation of vehicles using a ratio of 2:1 (control: LUCAS) with type of vehicle (vehicle or RRV) as strata. The following personnel will be blinded/unblinded to the allocation:

UNBLINDED	*BLINDED*
Vehicle clinicans cannot be blinded and will be aware of the allocation.	*Control room personnel will be blinded to the allocation of the vehicles, to ensure that no bias in whether a LUCAS or control vehicle is sent, which will give equal chance that a LUCAS or control will attend.*
Clinical trial co-ordinators/managers and data entry staff will be aware of the allocation due to the format of the CRF	*Patients themselves will be unaware of their treatment allocation at the time of the intervention- though they may subsequently be unblinded by relatives/friends.*
Statistician will produce and hold the treatment allocation.	*Chief Investigators and investigators (in the Trial Management Group) in the trial will not be aware of the allocation. No data reports based on outcomes are provided by treatment allocation for trial staff.*
	Research nurses assessing outcome at 3 and 12 months follow-up will be blinded to treatment group and will endeavour to maintain their blinding during the follow-up assessments.
	The Independent Data Monitoring Committee (IDMC) will be provided with data reports on outcomes detailed by

	intervention allocation, but the allocation will be blinded and should the IDMC deem necessary, the treatment allocation can be unblinded for them.
	The Trial Steering Committee do not seem any data report on the outcomes and therefore remain unblind to the allocation

Blinding

In the usual conventional clinical trial setting, it is important to ensure that patients, investigators and those collecting the data are unaware of the assigned treatment, so that they will not be influenced by that knowledge.

In PRE-FIT, it is not possible to blind the patient or the investigator from the allocated intervention. However, it is possible to ensure that the data management team are blinded from the allocation of the intervention.

Details of how the data management team will ensure blinding.