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

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Contents

SECTION 1: AIMS AND DESIGN OF THE TRIAL

1.1. Background

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

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

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

1.2. Research question

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

1.3. Rational of the trial

There is widespread interest in the use of intraosseous drug administration in cardiac arrest. In the UK, there is evidence of changing clinical practice. Data on file from the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry show use of the IO route doubled over four-years (16% 2014 to 33% in 2018). This is consistent with data from London Ambulance Service which found that expenditure on IO equipment doubled over two-years (£177k in 2017 to £ 364k in 2019). Data from North America shows large variability in IO use, with IO use ranging from 1 to 53% across study sites participating in the ALPS trial.[8]

Published data suggest the IO route may be equivalent in efficacy to the IV route. In view of a higher insertion success rate and reduced time to obtain vascular access with the IO route, it is possible that an IO first strategy may translate to improved patient outcomes. However, some studies suggest the IO route may be inferior to the IV route, leading to reduced plasma drug concentrations [7] and an overall reduction in survival.[9, 10].

Registered clinical trials in Singapore (NCT02088736), China (NCT04130984), Taiwan (NCT04135547) and Poland (NCT02305511) of IO use in OHCA do not resolve this uncertainty for the NHS because: (i) health care systems differ; (ii) the trials do not test an IO first strategy; and (iii) the sample sizes are too small to provide a definitive answer. In view of this ongoing uncertainty, the International Liaison Committee on Resuscitation, whilst continuing to suggest an IV first strategy, has highlighted the urgent need for a randomised controlled trial to determine the most effective approach.[6]

1.4. Trial design

Paramedic medication route is a multi-centre, pragmatic, individually randomised, parallel group, superiority trial and economic evaluation.

1.5. Objectives

Primary objective

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

Secondary objectives

Secondary trial objectives of the trial are:

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

1.6. Sample size

The target sample size 15,000 to detect a 1% difference in survival, with a power of 90% and a significance level of 5%.

1.7. Outcome measures

Primary outcome

- Survival at 30 days post randomisation

Secondary outcomes

- Any return of spontaneous circulation (ROSC)
- Time to ROSC
- Survived event (sustained ROSC at hospital handover)
- Survival to hospital discharge, 3 and 6 months
- Neurological function (measured by modified Rankin Scale (mRS) at discharge, 3, and 6 months)
- Health related quality of life (measured by EQ-5D-5L at 3 and 6 months)
- Hospital length of stay
- Critical care length of stay

Safety

- Adverse events (AEs)
- Serious adverse events (SAEs).

SECTION 2: MONITORING OF THE TRIAL (OPERATIONAL AND STATISTICAL)

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

1. Operational (logistical) and Process Management monitoring;
2. Statistical monitoring (assessment of bias – as stated in the protocol).

2.1. Operational (logistical) and trial management monitoring of patients

Recruitment of patients

Ten ambulance services and one air ambulance have been identified to randomise patients into the trial.

- A CONSORT diagram showing the flow chart of patients recruited in the study will be illustrated in Figure 1.

Inclusion/exclusion criteria

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

Inclusion criteria

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

Exclusion criteria

- Children (known or appear to be < 18 years)
- Known or apparent pregnancy
- Already have vascular access

Randomisation

- The point of randomisation will be the opening of the randomisation envelope (or an equivalent system, such as peelable stickers, scratch cards or sealed treatment packs).
- Randomisation by ambulance services and the balance between treatment arms (IO split by location, e.g. tibial and humerus) will be presented.

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

- A detailed summary showing the flow chart of patient status from recruitment to the end of study will be illustrated by treatment arm (Table 1 and Table 2).

Follow-up rates

- The follow-up rates will be derived from information presented by treatment arm (Table 1).

Protocol violations and deviations

- Protocol violations and deviations will be summarised by treatment arm (Table 3).

Withdrawals

Trial withdrawals may occur from the first hospital contact of patients. Patients who withdraw their consent will be logged on the database at the point that they communicate their intention to the trial team and no further contact will be made. All withdrawals will be summarised and analysed by treatment arm. Also all data up to the time of withdrawal will be retained in the analysis. National Health Service (NHS) records and remotely collected data up to 12 months post randomisation will continue to be used unless the patient explicitly declines permission for this in the consent or withdrawal form.

- Withdrawals will be summarised by treatment arm in Table 3.

Safety Data

- Treatment related adverse events (AEs) and serious adverse events (SAEs) will be summarised. See section 4.5 for details.

Unblinding

- Allocation unblinding during the trial will be summarised by treatment arm in Table 3.

2.2. Statistical monitoring during the trial

Assessment of bias

- Patient recruitment will be checked against the number of patients screened and patients met exclusion criteria.
- The characteristics of the enrolled patients and cardiac arrest events prior to EMS intervention will also be assessed by treatment arm.
- The data on the characteristics of patients and cardiac arrests (for assessment of bias) are reported to the DMC in each interim and final report. The DMC assesses these data for any variables that may exceed potential thresholds (as judged by the clinical experts). The final data will be summarised.

Non-compliance

- Based on DMC's comments in the first formal interim analysis meeting, we refined our definition of crossover: Treatment crossover is defined as the use of the route to which the patient is not randomised before two attempts have been made at the randomised route.
- To ensure the required sample size is achieved, we will monitor post-randomisation exclusion, non-compliance and their impact on the sample size/effect size that is required.

- Discontinuation of treatment (i.e. treatment withdrawal) is defined as treatment withdrawal before any attempt has been made at the randomised route. This excludes treatment crossover.
- Non-compliance is defined as any clinically relevant protocol deviation/violation.
- Total of crossover, discontinuation of treatment and non-compliance are compared by treatment by Chi-squared test.
- Treatment crossover, discontinuation of treatment and non-compliance are described in section 4.8 and summarised in Table 4.

Interim analysis

- Two formal interim analyses were planned at approximately 10% (n=1530) and 50% (n=7026) of total patient primary outcome data are available.
- The alpha spending method using O'Brien and Fleming approach is adopted to develop the stopping boundaries which will preserve the overall type I error rate of 5% and account for the fraction of data available as well as the unequal spacing in the interim analyses. The results will be plotted with resulting standardised z scores and p values.

Results will be presented in Figure 2.

SECTION 3: CLINICAL OUTCOMES AND ANALYSIS DATA

3.1. Outcome variables

Outcomes	Time point	Scoring
Primary outcome		
Survival	30 days post randomisation	Binary category: Alive; deceased
Secondary outcomes		
Return of spontaneous circulation (ROSC) at any time	Until admission and transfer of care to medical staff at the receiving hospital.	Binary category: Yes; No.
Time to ROSC	From 999 call to time of ROSC.	Time duration between 999 call and time of ROSC is summarised in minutes.
Sustained ROSC at hospital handover	Until admission and transfer of care to medical staff at the receiving hospital	Binary category: Yes; No.
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	Binary category: Alive; deceased

Modified Rankin Scale (mRS)	At discharge, 3- and 6-months post randomisation	mRS score is measured on a 7-point scale (from 0 (no symptom) to 6 (dead)). It is also summarised in binary category: Good (0-3) and Poor (4-6).
Favourable functional outcome	At discharge, 3- and 6-months post randomisation	Dichotomised mRS score: 0-3 is defined as favourable functional outcome; 4-6 is defined as unfavourable functional outcome.
Health related quality of life – EQ-5D-5L	At 3- and 6-months post randomisation	Summary of each item given and the VAS score (out of 100) summarised. The EQ-5D-5L utility score will be calculated using EQ-5D-5L UK Crosswalk value set. The EQ-5D-5L index score will be presented as a continuous outcome.
Hospital length of stay	From randomisation up to hospital discharge (survivors only). From randomisation up to death in hospital (for deceased patients).	Time during between randomisation and hospital discharge alive or dead in days. The duration for patients died on scene is calculated as the difference between randomisation and death dates.
Critical care length of stay	From randomisation up to the first critical care discharge. Recurrent critical care admissions are not counted (survivors only) From randomisation to death in ICU (for deceased patients). Data will be obtained from routine data.	Time during between randomisation and critical care unit discharge alive or dead in days. Patients not admitted to critical care unit are not counted.
Survival	To 3 months and 6 months post randomisation	Binary category: Alive; deceased
Adverse event (AE)	Up to hospital discharge	An AE is defined as any untoward medical occurrence in a participant participating in a clinical study and which does not necessarily have a causal relationship with the treatment/intervention.
Serious adverse event (SAE)	Up to hospital discharge	An SAE is not thought to be causally related to the research. The following events that are related to cardiac arrest and would be expected in patients undergoing

		attempted resuscitation should not be reported: - Death - Hospitalisation - Persistent or significant disability or incapacity - Organ failure

Tertiary outcomes

Process variables	Timepoint	Scoring/category
Initial aetiology	Until admission and transfer of care to medical staff at the receiving hospital	Medical (presumed cardiac); traumatic cause; drowning; drug overdose; electrocution; asphyxia.
Initial rhythm	Until admission and transfer of care to medical staff at the receiving hospital	Binary category: shockable and non-shockable. Nominal categories: VF; pulseless VT; asystole; PEA/EMD; bradycardia; AED shockable; AED non-shockable. Shockable rhythm includes VT, VT and AED shockable, and non-shockable rhythm includes Asystole, PEA/EMD, Bradycardia and AED non-shockable.
Location	Until admission and transfer of care to medical staff at the receiving hospital	Home/residence; Industrial/Workplace; Sport/recreation event; Street/Highway; Public building; Assisted living/nursing home; Education Institution; Not known/not recorded; Other.
Witnessed	Until admission and transfer of care to medical staff at the receiving hospital	Unwitnessed; EMS witnessed; bystander witnessed.
Bystander CPR	Up to EMS arrival at the scene	Yes; no.
Response time	Up to EMS arrival at the scene	Time duration between 999 call and EMS arrival is summarised in minutes. For EMS witnessed cases, time is set to 0 minute.
Time from EMS call to gain access	Up to EMS gain vascular access	Time duration between 999 call and EMS gain vascular

		access is summarised in minutes. For EMS witnessed cases, time up to EMS arrival is set to 0 minute.
Time from EMS call to drug given	Up to drug administration	Time duration between 999 call and EMS administration of adrenaline is summarised in minutes. For EMS witnessed cases, time up to EMS arrival is set to 0 minute.
Time from EMS arrival at scene until EMS transport	Up to EMS left the scene	Time duration between EMS arrival at the scene and left scene is summarised in minutes.
Time from EMS arrival at scene to hospital	Up to EMS arrival at hospital	Time duration between EMS left the scene and arrival at hospital is summarised in minutes.
Patients transported to hospital	Up to transfer of care to medical staff at receiving hospital	Yes; no.

3.2. Type of populations

Intention to treat population

The primary and secondary analyses will be performed for the Intention to treat (ITT) population. 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.

3.3. Analysis datasets

Usually there are two datasets used for the statistical analysis: (a) Observed and (b) Imputed. Observed dataset will be used for the ITT analysis of primary and secondary outcomes and tertiary data. For the primary outcome and data collected prior to hospital discharge only the observed datasets will be used for the ITT 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).

An imputed dataset, where possible, will be made for completeness for survival at 30 days and functional outcomes in the sensitivity analysis.

Observed dataset

This will comprise of all the data observed (including follow-up) with missing values.

Imputed dataset

We will impute missing data of survival at 30 days and favourable functional outcome (dichotomised mRS) at hospital discharge, 3 and / or 6 months follow-up for a sensitivity analysis. Assuming missing at random (MAR), we will use multiple imputation by chained equation (MICE) [11], for imputation of the outcomes. In general, 5-10 imputed datasets are usually sufficient but more may be needed in the unlikely event of high missingness level. To assess the robustness of the imputation results under the missing not at random (MNAR) assumption, we will conduct a tipping point analysis [12]. It will use a shift parameter to adjust the proportion of favourable outcome imputed in the missing cases. A series of imputed datasets will be generated and used to estimate the treatment effect over the range of shift. The tipping point is identified when the statistical conclusion is altered. If the relevant outcome summaries are deemed as clinically plausible, the findings of the complete case analysis could be questionable.

The missing survival data will also be imputed as survived and deceased in the best and worst scenario.

In addition, we will use the following imputation methods for missing functional data:

1. Extrapolation/interpolation: missing functional data will be derived using the sequence of collected mRS data at the other follow-ups.
2. Last value carried forward/next value carried backward: missing functional data will be imputed using the last observed or next observed value, depending on the missing pattern.
3. Best scenario: all missing functional data will be imputed as favourable outcome.
4. Worst scenario: all missing functional data will be imputed as unfavourable outcome.

SECTION 4:MAIN STATISTICAL ANALYSIS AND THE ESTIMAND FRAMEWORK

4.1. General considerations

In general, continuous baseline and outcome data will be summarised with descriptive statistics, including n, mean, standard deviation, median, interquartile range and n of missing data. The 95% confidence interval of median of continuous outcomes will also be reported. Categorical baseline and outcome data will be summarised with frequency counts and percentages. In addition, graphical presentation will be made for several variables that are specified individually. In addition, outcome data will be compared by treatment arms. Odds ratio (OR) with 95% confidence interval (CI) will be reported for categorical outcomes and mean difference with 95% CI will be reported for continuous outcomes, unless stated otherwise. For survival analysis, hazard ratio (HR) with 95% Cis will be reported. A two-sided p value <0.05 is considered statistically significant, unless otherwise stated. The statistical analysis will be carried out using SAS, STATA or R.

4.2. Characteristics of patients and cardiac arrests

At randomisation

The characteristics of enrolled patients and cardiac arrest data prior to EMS trial drug administration are summarised by IO and IV treatment.

Post randomisation

The characteristics of enrolled patients and cardiac arrest data from EMS trial drug administration are summarised by IO and IV treatment.

4.3. Primary outcome and the estimand framework

In line with the ICH E9 (R1) addendum on Estimand and sensitivity analyses in clinical trials [13], the following defines the Estimand framework, in relation to the primary outcome.

Estimand attribute	**Description**
Objective	To evaluate the effectiveness of paramedic administered intravenous access or intraosseous access first strategy in the treatment of an OHCA (out of hospital cardiac arrest), from randomisation to 30 day post randomisation assessment.
Treatment conditions	Intravenous (IV) access first strategy vs intraosseous (IO) access first strategy when paramedics administer adrenaline.
Population	Non-pregnant adult (≥ 18 years) participants, treated by the attending paramedic (pre-hospital), where vascular access for cardiac arrest drugs administration is required
Variable (primary outcome)	Survival at 30 days post randomisation, from randomisation. The point of randomisation is defined as the time when the randomisation envelope (or an equivalent system, such as peelable stickers, scratch cards or sealed treatment packs) is opened.
Summary measure	Proportion of individuals who have survived to 30 days post randomisation.
Handling Intercurrent events	Post-randomisation events which may affect the interpretation or occurrence of the primary outcome include: ICE 1: discontinuation of treatment before initiation of the allocated treatment ICE 2: Treatment crossover
Strategies for handling intercurrent events	ICE 1: (a) *Treatment policy-* analysis as observed ICE 2: *Principal stratum strategy –* analysis using inverse probability censoring weighted (IPCW) method

4.4. Primary outcome analysis

The analysis will be carried out using binary logistic regression on an ITT basis with covariate adjustment for: age, sex, EMS witnessed cardiac arrest versus bystander witnessed versus not witnessed, bystander CPR (yes; no), initial rhythm (shockable versus non-shockable), time from 999 call to drug administration, aetiology of cardiac arrest (medical versus nonmedical). The significance level will be corrected for the interim analysis performed to control the overall p value of 0.05. Results will be presented in odds ratio and 95% CI (Table 6).

4.5. Secondary outcome analyses

- **Survival at 30 days**

Secondary analysis for the primary outcome will be summarised using unadjusted analysis. Results will be presented in Table 6.

The survival time data will also be plotted by treatment arm using Kaplan-Meier curve and compared using log rank test. Patients who are lost to follow-up or survive beyond 30 days will be censored (Figure 3).

The significance level will only be corrected for the interim analysis performed in the unadjusted analysis.

- **Any return of spontaneous circulation (ROSC)**

All survival outcomes will be treated as a dichotomous without any censoring. Patient ROSC will be summarised and analysed using ordinary logistic regression model on the basis of ITT population. Analysis will be carried out with and without adjustment for covariates as detailed in Section 4.7. Results will be presented in Table 7.

- **Time to ROSC**

Time to any ROSC will be analysed using Cox regression model on the basis of ITT with and without adjustment for covariates as detailed in Section 4.7. The proportional hazards assumption will be tested graphs (e.g. plots of log (-log (survival function)) versus time). Results will be presented in Table 8.

The time to ROSC data will also be plotted by treatment arm using Kaplan-Meier curve and compared using log rank test (Figure 4). Patients who are lost to follow-up or do not achieved ROSC will be censored.

- **Sustained ROSC at hospital handover**

Sustained ROSC will be analysed in the same way as any ROSC. Results will be presented in Table 7.

The time to sustained ROSC data, represented by time to hospital arrival, will also be plotted by treatment arm using Kaplan-Meier curve and compared using log rank test (Figure 5). Patients who are lost to follow-up or do not achieve ROSC at handover will be censored.

- **Survival to hospital discharge, 3 and 6 months**

Survival to hospital discharge will be analysed in the same way as detailed for any ROSC. Results will be presented in Table 7.

Survival to hospital discharge, 3 and 6 months and will also be plotted by treatment arm using Kaplan-Meier curve and compared using log rank test. Patients who are lost to follow-up or survive to each follow-up time point will be censored. Results will be presented in Figure 7.

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

The modified Rankin Scale (mRS) at hospital discharge, 3 and 6 months follow-up will be summarised in two approaches: ordinal and binary (0-3 versus 4-6). The ordinal and binary functional outcomes will be summarised and analysed using ordinal and binary logistic regression models, respectively, with and without adjustment for covariates as detailed in this section. If the proportional odds assumption cannot be held, alternative methods will be sought after, such as sliding dichotomy, nominal logistic regression and Poisson analyses. Results will be presented in Table 9.

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

The EQ-5D-5L visual analogy score (VAS) and utility score at 3 and 6 months follow-up will be graphically presented and analysed using linear regression model on the basis of ITT with and without adjustment for covariates as detailed in this section. Results will be presented in Table 10.

- **Critical care length of stay**

Critical care length of stay will be summarised and analysed using linear regression model on the basis of ITT with and without adjustment for covariates as detailed in Section 4.7. Results will be presented in Table 10.

Survival to ICU discharge will also be plotted by treatment arm using Kaplan-Meier curve and compared using log rank test. Patients who are lost to follow-up or survive to discharge will be censored. Results will be presented in Figure 7.**Figure 7**

- **Hospital length of stay**

Length of stay in hospital will be summarised and analysed using linear regression model on the basis of ITT with and without adjustment for covariates as detailed in Section 4.7. Results will be presented in Table 10 and Figure 7.

- **Adverse events and serious adverse events**

Adverse events and SAEs will be summarised regarding their type, causality and CTCAE grade. The rate of Aes and SAEs will be compared using unadjusted Poisson regression. Results will be presented in Table 11 to Table 14.

4.6. Subgroup analyses

Prespecified subgroup analysis will be conducted on:

- Age

- Sex
- Witnessed cardiac arrest versus not witnessed
- Bystander CPR (yes; no)
- Initial rhythm (shockable; non-shockable)
- Time to 999 call to ambulance arrival
- Aetiology of cardiac arrest (presumed cardiac versus non cardiac)

These sub-group analyses will be conducted in the observed dataset on the basis of ITT population. They will involve modelling the
Treatment by subgroup interaction. Thus the analyses will use unadjusted logistic regression model. A forest plot with OR (95% CI) of each subgroup will be presented (Figure 6).

Additional subgroup analysis of co-enrolment may be carried out to explore the possible interaction with the trial. Details of the co-enrolment will be provided in the final analysis.

4.7. Exploratory analyses

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

The analyses will be based on the following pairwise comparisons:

a. IO (humeral) versus IO (tibial)
b. IO (humeral) versus IV
c. IO (tibial) versus IV.

Each outcome will be analysed and reported in the same way specified in section 4.4 and 4.5. P value will be adjusted for multiplicity using Bonferroni correction. Results will be presented in Table 15 to Table 22 and Figure 7.

A graphical display of the odds ratios of survival versus time-to-access, using fractional polynomial methods. The odds ratios will be derived from regression models with the interaction of timing x treatment (IO(tibial)/IO(humeral)/IV)) and the graphical plot will allow us to assess the odds of survival over time, for each of the interventions. We will present this plot with 95% confidence bands. Results will be presented in Figure 8.

4.8. Sensitivity analyses

- **Fragility index or reverse fragility index**

We will test the sensitivity of the results using Fragility Index (FI) or Reverse Fragility Index (RFI) for the primary outcome.[14, 15] The minimum number needed to change the significant (non-

significant) primary analysis result to non-significant (significant) will be reported. Results will be presented in Table 23.

- **Imputed data**

If imputed data are generated, we will conduct sensitivity analysis for the imputed outcome data in an ITT approach. The outcomes will be summarised and analysed using the binary logistic regression without adjustment for covariates. Results will be presented in Table 24.

- **Treatment crossover**

Unplanned crossovers across the interventions will lead to contamination of the initial randomised intervention due to a mixing of effects in the outcomes, reducing the power of the study. This is further complicated by the fact that crossover are often a very selective process whereby patients who have their treatment switched have a different prognosis that those who do not. We will use inverse probability censoring weighted (IPCW) analysis [16] to account for unplanned crossovers, using the primary outcome measure. Results will be presented in Table 25.

- **Discontinuation of treatment**

Discontinuation of treatment will be presented in Table 4.

SECTION 5: ADDITIONAL STATISTICAL ANALYSIS

5.1. Bayesian analysis

Our trial was designed based on the evidence published in the recent years. However, the potential variations of proposed effect size in the observed data and slow recruitment may pose a risk to a statistically powered analysis. Therefore, we will carry out an unadjusted Bayesian logistic analysis of the primary outcome to aid the interpretation of the trial data.

Bayesian analysis is sensitive to the choice of priors. Hence, we will use a range of priors of the treatment difference, including non-informative, informative, enthusiastic and sceptical priors. The distribution of these priors will be decided by recent clinical evidence and clinical experts in the trial team.

We will report the posterior mean and 95% credible interval of the estimated risk difference (i.e. treatment difference). No fixed success criterion will be set as this analysis is for exploratory purpose. Instead, we will report the probability of absolute clinically important risk difference by 1%, 2% and 3%. The prior and posterior distribution of the differences will be plotted. Results will be presented in Table 26 and Figure 9 to Figure 10.

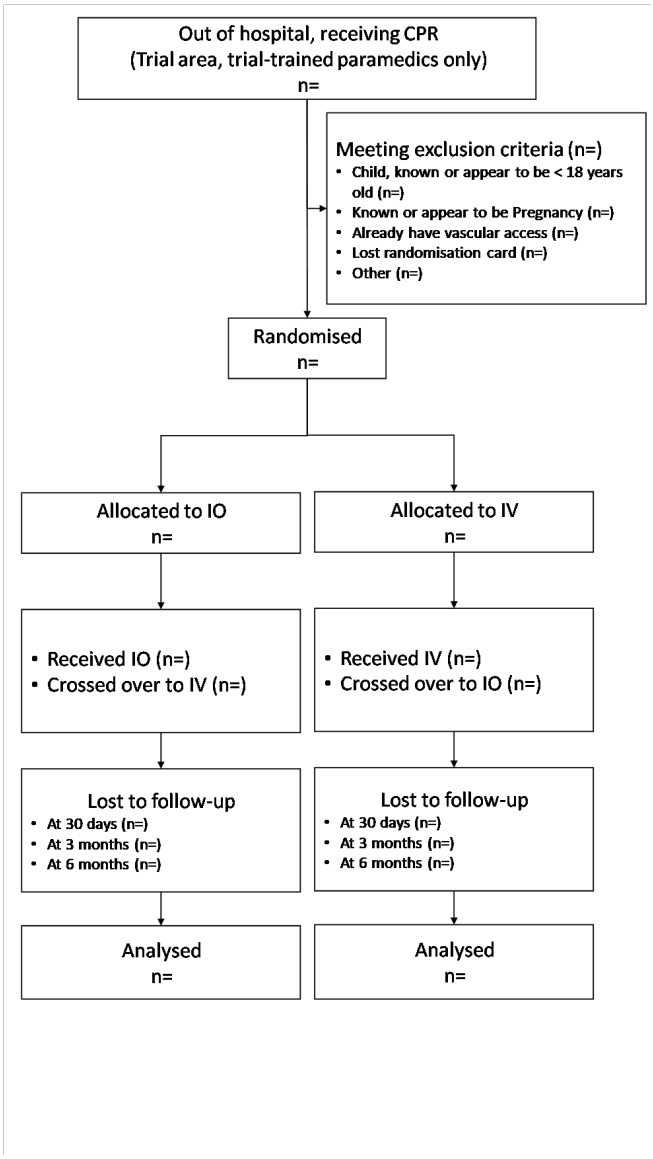
SECTION 6: REFERENCES

1. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation. 2017;110:133-40. Epub 2016/11/21. doi: 10.1016/j.resuscitation.2016.10.030. PubMed PMID: 27865775.
2. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC, Callaway CW. Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest: Implications for Prolonging or Terminating Resuscitation. Circulation. 2016;134(25):2084-94. Epub 2016/10/21. doi: 10.1161/CIRCULATIONAHA.116.023309. PubMed PMID: 27760796; PubMed Central PMCID: PMCPMC5173423.
3. Smith CM, Wilson MH, Ghorbangholi A, Hartley-Sharpe C, Gwinnutt C, Dicker B, et al. The use of trained volunteers in the response to out-of-hospital cardiac arrest - the GoodSAM experience. Resuscitation. 2017;121:123-6. Epub 2017/10/29. doi: 10.1016/j.resuscitation.2017.10.020. PubMed PMID: 29079507.
4. National Health Service. The NHS Long Term Plan 2019. 2019.
5. Soar J, Berg KM, Andersen LW, Bottiger BW, Cacciola S, Callaway CW, et al. Adult Advanced Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2020;156:A80-A119. Epub 2020/10/26. doi: 10.1016/j.resuscitation.2020.09.012. PubMed PMID: 33099419; PubMed Central PMCID: PMCPMC7576326.
6. Soar J, Bottiger BW, Carli P, Couper K, Deakin CD, Djarv T, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation. 2021;161:115-51. Epub 2021/03/29. doi: 10.1016/j.resuscitation.2021.02.010. PubMed PMID: 33773825.
7. Booth SJ, C.; Soar, J; Siriwardena, AN; Fothergill, R; Spaight, R; Perkins, GD;, editor Prehospital adrenaline administration for out-of-hospital cardiac arrest: The picture in England and Wales. RESUSCITATION 2018; 2018: Resuscitation.
8. Daya MR, Leroux BG, Dorian P, Rea TD, Newgard CD, Morrison LJ, et al. Survival After Intravenous Versus Intraosseous Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Shock-Refractory Cardiac Arrest. Circulation. 2020;141(3):188-98. Epub 2020/01/17. doi: 10.1161/CIRCULATIONAHA.119.042240. PubMed PMID: 31941354; PubMed Central PMCID: PMCPMC7009320.
9. Zhang Y, Zhu J, Liu Z, Gu L, Zhang W, Zhan H, et al. Intravenous versus intraosseous adrenaline administration in out-of-hospital cardiac arrest: A retrospective cohort study. Resuscitation. 2020;149:209-16. Epub 2020/01/27. doi: 10.1016/j.resuscitation.2020.01.009. PubMed PMID: 31982506.
10. Kawano T, Grunau B, Scheuermeyer FX, Gibo K, Fordyce CB, Lin S, et al. Intraosseous Vascular Access Is Associated With Lower Survival and Neurologic Recovery Among Patients With Out-of-Hospital Cardiac Arrest. Ann Emerg Med. 2018;71(5):588-96. Epub 2018/01/10. doi: 10.1016/j.annemergmed.2017.11.015. PubMed PMID: 29310869.

11. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res. 2011;20(1):40-9. Epub 2011/04/19. doi: 10.1002/mpr.329. PubMed PMID: 21499542; PubMed Central PMCID: PMCPMC3074241.
12. Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat. 2013;12(6):337-47. Epub 2013/01/08. doi: 10.1002/pst.1549. PubMed PMID: 23292975.
13. Adams TS, Blouin D, Johnson D. Effects of tibial and humerus intraosseous and intravenous vasopressin in porcine cardiac arrest model. Am J Disaster Med. 2016;11(3):211-8. Epub 2017/01/31. doi: 10.5055/ajdm.2016.0241. PubMed PMID: 28134420.
14. Khan MS, Ochani RK, Shaikh A, Usman MS, Yamani N, Khan SU, et al. Fragility Index in Cardiovascular Randomized Controlled Trials. Circ Cardiovasc Qual Outcomes. 2019;12(12):e005755. Epub 2019/12/12. doi: 10.1161/CIRCOUTCOMES.119.005755. PubMed PMID: 31822121; PubMed Central PMCID: PMCPMC7962007.
15. Khan MS, Fonarow GC, Friede T, Lateef N, Khan SU, Anker SD, et al. Application of the Reverse Fragility Index to Statistically Nonsignificant Randomized Clinical Trial Results. JAMA Netw Open. 2020;3(8):e2012469. Epub 2020/08/07. doi: 10.1001/jamanetworkopen.2020.12469. PubMed PMID: 32756927; PubMed Central PMCID: PMCPMC7407075 from Abbott, AstraZeneca, Amgen, Bayer, Edwards, Janssen, Merck, and Medtronic outside the submitted work as well as being associate editor of JAMA Cardiology. Dr Friede reported receiving personal fees from Bayer, Novartis, Vifor, Enanta, Daiichy Sankyo, Johnson & Johnson, Boehringer Ingelheim, Roche, Fresenius Kabi, LivaNova, Galapagos, Penumbra, and Relaxera outside the submitted work. Dr Anker reported receiving grants and personal fees from Vifor and AV-Pharma as well as personal fees from Bayer, Boehringer Ingelheim, Novartis, Impulse Dynamics, and Servier outside the submitted work. Dr Butler reported receiving personal fees as a consultant from Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Berlin Cures, Boehringer Ingelheim, Bristol-Myers Squib, CVRx, G3 Pharmaceutical, Innolife, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, SC Pharma, V-Wave Limited, and Vifor outside the submitted work. No other disclosures were reported.
16. Dodd S, Williamson P, White IR. Adjustment for treatment changes in epilepsy trials: A comparison of causal methods for time-to-event outcomes. Stat Methods Med Res. 2019;28(3):717-33. Epub 2017/11/10. doi: 10.1177/0962280217735560. PubMed PMID: 29117780; PubMed Central PMCID: PMCPMC6419234.

APPENDIX A: Figures

Figure 1. CONSORT diagram



Note: IV, intravenous access. IO, intraosseous access.

APPENDIX B: Tables

SECTION 1 Trial operational and patient baseline characteristics

Table 1. Patient status from prior to hospitalisation to the end of study

	Treatment arm		
	IO	**IV**	**TOTAL**
Status at pre-hospital			
Screened	-	-	
Met exclusion criteria	-	-	
Randomised			
Allocated treatment			
Transported to hospital			
Achieved ROSC at anytime			
Status in hospital			
Achieved sustained ROSC at hospital handover			
Admitted to ICU			
Survived to ICU discharge			
Died in ICU			
Still in ICU			
Survived to hospital discharge			
Died in hospital			
Still in hospital			
- Withdrawal during hospital stay			
Status at fixed follow-ups			
Survived at 30 days			
Died in 30 days			
- Withdrawal within 30 days			
Survived between 30 days to 3 months			
Died in between 30 days to 3 months			
- Withdrawal between 30 days to 3 months			
Survived between 3 and 6 months			
Died between 3 and 6 months			
- Withdrawal between 3 and 6 months			

Note: patients may stay in ICU/hospital for more than the fixed follow-up timepoints. Hence, the numbers in hospital stay may not add up to match the numbers in the fixed follow-up.

Table 2. Randomisation balance by ambulance service and drug administration location

Ambulance service	**IO**				**IV**	**TOTAL**
	Humerus	Tibial	Other or missing	**Total**	**Total**	**(Humerus % / Tibial %)***
London Ambulance Service						
Welsh Ambulance Service						
North East Ambulance Service						
North West Ambulance Service						
East Midlands Ambulance Service						
West Midlands Ambulance Service						
East of England Ambulance Service						
South East Coast Ambulance Service						
South Central Ambulance Service						
South Western Ambulance Service						
Air Ambulance Service						

*Note: *, percentage of humerus and tibial routes are calculated based on the number of patients randomised to the IO arm. The percentages do not necessarily add up to 100% because of missing data and crossover.*

Table 3. Protocol deviations, violations, withdrawal and unblinding by treatment arm

		IO	IV	TOTAL
Deviations	Reason 1			
	Reason 1			
	Reason 2			
	Total			
Violations	Reason 1			
	Reason 1			
	Reason 2			
	Total			
Withdrawal	Withdrawn from patient reported outcome measures			

	Withdrawn from collection and data linkage			
	Withdrawal from future approved research			
	Withdrawn completely from follow-up			
Unblinding	Unblinded			

Table 4. Non-compliance by treatment arm

	IO	IV	TOTAL/p value
Non-compliance			
London Ambulance Service			
Welsh Ambulance Service			
North East Ambulance Service			
North West Ambulance Service			
East Midlands Ambulance Service			
West Midlands Ambulance Service			
East of England Ambulance Service			
South East Coast Ambulance Service			
South Central Ambulance Service			
South Western Ambulance Service			
Air Ambulance Service			
Total			
Discontinuation of treatment			
London Ambulance Service			
Welsh Ambulance Service			
North East Ambulance Service			

North West Ambulance Service			
East Midlands Ambulance Service			
West Midlands Ambulance Service			
East of England Ambulance Service			
South East Coast Ambulance Service			
South Central Ambulance Service			
South Western Ambulance Service			
Air Ambulance Service			
Total			
Treatment crossover			
London Ambulance Service			
Welsh Ambulance Service			
North East Ambulance Service			
North West Ambulance Service			
East Midlands Ambulance Service			
West Midlands Ambulance Service			
East of England Ambulance Service			
South East Coast Ambulance Service			
South Central Ambulance Service			
South Western Ambulance Service			
Air Ambulance Service			
Total			

Note: Discontinuation of treatment is defined as treatment withdrawal before any attempt has been made at the randomised route. Treatment crossover is defined as the use of the route to which the patient is not randomised before two attempts have been made at the randomised route. Chi-squared test is carried out at the overall level.

Table 5. Patient and event characteristics by treatment arm

		IO	IV	TOTAL
Age	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			
Sex	Male			
	Female			
	Missing			

Location (Utstein style)	Home/residence			
	Industrial/Workplace			
	Sport/recreation event			
	Street/Highway			
	Public building			
	Assisted living/nursing home			
	Education Institution			
	Not known/not recorded			
	Other			
	Missing			
Initial rhythm	*Shockable rhythm*			
	Shockable - VF			
	Pulseless - VT			
	AED shockable			
	Non-shockable rhythm			
	PEA			
	Asystole			
	AED non-shockable			
	Not known/not recorded			
	Missing			
Initial aetiology	Medical			
	Trauma			
	Drowning			
	Overdose			
	Asphyxial			
	Electrocution			
	Not known/not recorded			
	Missing			
Occurrence witnessed	Unwitnessed			
	EMS witnessed			
	Bystander witnessed			
	Not known/not recorded			
	Missing			
Bystander commenced CPR	Yes			
	No			
	Not applicable (EMS witnessed)			
	Not known/not recorded			
	Missing			
PAD used	Yes			
	No			
	Not applicable (EMS witnessed)			
	Not known/not recorded			
	Missing			
Supraglottic Airway	Yes			
	No			
	Not known/not recorded			

	Withdrawal			
	Missing			
Tracheal tube	Yes			
	No			
	Not known/not recorded			
	Missing			
Time from 999 call to Arrival at scene (minutes)	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			
Time from Arrival at scene to gain vascular access (minutes)	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			
Time from 999 call to gain vascular access (minutes)	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			
Time from 999 call to Administration of drug (minutes)	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			
Time from Arrival at scene to EMS transport (minutes)	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			
Time from 999 call to Hospital arrival (minutes)	N			
	Mean			
	Std. Deviation			
	Median			
	IQR			
	Missing			

Note: PAD, public access defibrillators.

SECTION 2 Main analysis

Table 6. Unadjusted and adjusted analysis of survival at 30 days (Intention to treat, observed data)

		IO	IV	TOTAL	UNADJUSTED ANALYSIS OR (95% CI), p value	ADJUSTED ANALYSIS* OR (95% CI), p value
Survival at 30 days	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		

Note: OR, odds ratio. *, primary analysis, adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 7. Unadjusted and adjusted analysis of secondary survival outcomes (Intention to treat)

		IO	IV	TOTAL	UNADJUSTED ANALYSIS OR (95% CI), p value	ADJUSTED ANALYSIS* OR (95% CI), p value
Anytime ROSC	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		
Sustained ROSC at hospital handover	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		
Survival to hospital discharge	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		

Survival at 3 months	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		
Survival at 6 months	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		

Note: OR, odds ratio. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 8. Unadjusted and adjusted analysis of Time to survival outcomes (Intention to treat)

		IO	IV	TOTAL	UNADJUSTED ANALYSIS HR (95% CI), p value	ADJUSTED ANALYSIS* HR (95% CI), p value
Time to ROSC (minutes)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Survival to sustained ROSC at hospital handover (minutes)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		

	Missing	xx	xx	xx		
Critical care length of stay (days)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Hospital length of stay (days)[#]	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Survival to 30 days (days)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Survival to 3 months (days)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Survival to 6 months (days)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		

	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		

Note: SD, standard deviation. IQR, interquartile range. HR, hazard ratio. #, analysis includes all patients. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 9. Unadjusted and adjusted analysis of neurological function (Intention to treat)

		IO	IV	TOTAL	UNADJUSTED ANALYSIS OR (95% CI), p value	ADJUSTED ANALYSIS* OR (95% CI), p value
Modified Rankin Scale at discharge (ordinal)#	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)		
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)		
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)		
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)		
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)		
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)		
	Unknown	xx	xx	xx		
Modified Rankin Scale at discharge (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		
Modified Rankin Scale at 3 months (ordinal)#	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)		
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)		

	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)		
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)		
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)		
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)		
	Unknown	xx	xx	xx		
Modified Rankin Scale at 3 months (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		
Modified Rankin Scale at 6 months (ordinal)	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)		
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)		
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)		
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)		
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)		
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)		
	Unknown	xx	xx	xx		
Modified Rankin Scale at 6 months (binary)#	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)		
	Missing	xx	xx	xx		

Note: OR, odds ratio. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest. #, proportional odds assumption is tested using score test.

Table 10. Unadjusted and adjusted analysis of length of stay and health related quality of life (Intention to treat)

		IO	IV	TOTAL	UNADJUSTED ANALYSIS	ADJUSTED ANALYSIS*

					MD (95% CI), p value	MD (95% CI), p value
Critical care length of stay (survivors)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Critical care length of stay (deceased)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Hospital length of stay (survivors)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
Hospital length of stay (deceased)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
EQ-5D-5L index score at 3 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		

	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
EQ-5D-5L visual analogue scale at 3 months	N	xx	xx	xx	x.x (x.x, x.x)	x.x (x.x, x.x)
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
EQ-5D-5L index score at 6 months	N	xx	xx	xx	x.x (x.x, x.x)	x.x (x.x, x.x)
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		
EQ-5D-5L visual analogue scale at 6 months	N	xx	xx	xx	x.x (x.x, x.x)	x.x (x.x, x.x)
	Mean	xx	xx	xx		
	Std. Deviation	xx	xx	xx		
	Median	xx	xx	xx		
	IQR	xx - xx	xx - xx	xx - xx		
	Missing	xx	xx	xx		

Note: SD, standard deviation. IQR, interquartile range. MD, mean difference. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 11. Summary of adverse events

		IO	IV	TOTAL
Relationship to trial intervention (causality)	Definitely	x (x%)	x (x%)	x (x%)
	Probably	x (x%)	x (x%)	x (x%)
	Possibly	x (x%)	x (x%)	x (x%)
Time of event	At cardiac arrest	x (x%)	x (x%)	x (x%)
	During hospital stay	x (x%)	x (x%)	x (x%)
	At hospital discharge	x (x%)	x (x%)	x (x%)
N of AE		x	x	x
N of AE per 1000 patients		x.x	x.x	x.x
Unadjusted analysis IRR (95% CI), p value				

Table 12. List of adverse events by treatment arm

Number	Details of AE
IO	
1	
…	
IV	
1	
….	

Table 13. List of serious adverse events by treatment arm

Number	Details of SAE
IO	
1	
…	
IV	
1	
….	

Table 14. Summary of serious adverse events

		IO	IV	TOTAL
Type of event	Results in death			
	Is life-threatening			
	Requires inpatient hospitalization or causes prolongation of existing hospitalization			
	Results in persistent or significant disability/incapacity			
	May have caused a congenital anomaly/birth defect			
	Requires medical intervention to prevent one of the above or is otherwise medically significant			
Relationship to trial intervention (causality)	Definitely			
	Probably			
	Possibly			
	Unlikely			
	Unrelated			
	Outstanding			
Time of event	At cardiac arrest			
	During hospital stay			
	At hospital discharge			
	Outstanding			
N of SAE				
N of SAE per 1000 patients				
Unadjusted analysis				

IRR (95% CI), p value				

Table 15. Exploratory analysis of survival outcomes (Intention to treat, unadjusted)

		IO tibial	IO humerus	IV	UNADJUSTED ANALYSIS IO tibial vs IO humerus OR (95% CI), p value	UNADJUSTED ANALYSIS IO tibial vs IV OR (95% CI), p value	UNADJUSTED ANALYSIS IO humerus vs IV OR (95% CI), p value
Anytime ROSC	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Sustained ROSC at hospital handover	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Survival to hospital discharge	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Survival at 30 days	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Survival at 3 months	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			

	Missing	xx	xx	xx			
Survival at 6 months	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			

Note: p value adjusted for multiplicity using Bonferroni correction.

Table 16. Exploratory analysis of survival outcomes (Intention to treat, adjusted)

		IO tibial	IO humerus	IV	ADJUSTED ANALYSIS* IO tibial vs IO humerus OR (95% CI), p value	ADJUSTED ANALYSIS* IO tibial vs IV OR (95% CI), p value	ADJUSTED ANALYSIS* IO humerus vs IV OR (95% CI), p value
Anytime ROSC	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Sustained ROSC at hospital handover	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Survival to hospital discharge	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Survival at 30 days	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
	Yes	xx (xx%)	xx (xx%)	xx (xx%)			

Survival at 3 months	No	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Missing	xx	xx	xx			
Survival at 6 months	Yes	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			

Note: p value adjusted for multiplicity using Bonferroni correction. OR, odds ratio. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 17. Exploratory analysis of survival time outcomes (Intention to treat, unadjusted)

		IO tibial	IO humerus	IV	UNADJUSTED ANALYSIS IO tibial vs IO humerus HR (95% CI), p value	UNADJUSTED ANALYSIS IO tibial vs IV HR (95% CI), p value	UNADJUSTED ANALYSIS IO humerus vs IV HR (95% CI), p value
Time to ROSC (minutes)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival to sustained ROSC at hospital handover (minutes)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			

	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Critical care length of stay (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Hospital length of stay (days)[#]	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival at 30 days (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival at 3 months (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival at 6 months (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			

	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			

Note: SD, standard deviation. IQR, interquartile range. HR, hazard ratio. p value adjusted for multiplicity using Bonferroni correction. #, analysis includes all patients.

Table 18. Exploratory analysis of survival time outcomes (Intention to treat, adjusted)

		IO tibial	IO humerus	IV	ADJUSTED ANALYSIS* IO tibial vs IO humerus HR (95% CI), p value	ADJUSTED ANALYSIS* IO tibial vs IV HR (95% CI), p value	ADJUSTED ANALYSIS* IO humerus vs IV HR (95% CI), p value
Time to ROSC (minutes)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival to sustained ROSC at hospital handover (minutes)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
	N	xx	xx	xx			

Critical care length of stay (days)	Mean	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Hospital length of stay (days)[#]	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival at 30 days (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival at 3 months (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Survival at 6 months (days)	N	xx	xx	xx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			

Note: SD, standard deviation. IQR, interquartile range. HR, hazard ratio. p value adjusted for multiplicity using Bonferroni correction. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest. #, analysis includes all patients.

Table 19. Exploratory analysis of functional outcomes (Intention to treat, unadjusted)

		IO tibial	IO humerus	IV	UNADJUSTED ANALYSIS IO tibial vs IO humerus OR (95% CI), p value	UNADJUSTED ANALYSIS IO tibial vs IV OR (95% CI), p value	UNADJUSTED ANALYSIS IO humerus vs IV OR (95% CI), p value
Modified Rankin Scale at discharge (ordinal)#	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)			
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)			
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)			
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)			
	Unknown	xx	xx	xx			
Modified Rankin Scale at discharge (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Modified Rankin Scale at 3 months (ordinal)#	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)			

	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)			
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)			
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)			
	Unknown	xx	xx	xx			
Modified Rankin Scale at 3 months (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Modified Rankin Scale at 6 months (ordinal) #	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)			
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)			
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)			
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)			
	Unknown	xx	xx	xx			
Modified Rankin Scale at 6 months (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			

Note: OR, odds ratio. #, proportional odds assumption is tested using score test.

Table 20. Exploratory analysis of functional outcomes (Intention to treat, adjusted)

		IO tibial	IO humerus	IV	ADJUSTED ANALYSIS* IO tibial vs IO humerus OR (95% CI), p value	ADJUSTED ANALYSIS* IO tibial vs IV OR (95% CI), p value	ADJUSTED ANALYSIS* IO humerus vs IV OR (95% CI), p value
Modified Rankin Scale at discharge (ordinal)#	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)			
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)			
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)			
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)			
	Unknown	xx	xx	xx			
Modified Rankin Scale at discharge (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Modified Rankin Scale at 3 months (ordinal)#	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)			
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)			
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)			
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)			

	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)			
	Unknown	xx	xx	xx			
Modified Rankin Scale at 3 months (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			
Modified Rankin Scale at 6 months (ordinal) #	0 - No symptoms	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	1 - No significant disability	xx (xx%)	xx (xx%)	xx (xx%)			
	2 - Slight disability	xx (xx%)	xx (xx%)	xx (xx%)			
	3 - Moderate disability	xx (xx%)	xx (xx%)	xx (xx%)			
	4 - Moderately severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	5 - Severe disability	xx (xx%)	xx (xx%)	xx (xx%)			
	6 - Dead	xx (xx%)	xx (xx%)	xx (xx%)			
	Unknown	xx	xx	xx			
Modified Rankin Scale at 6 months (binary)	Favourable (0-3)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx	x.xxx (x.xxx, x.xxx), 0.xxx
	Unfavourable (4-6)	xx (xx%)	xx (xx%)	xx (xx%)			
	Missing	xx	xx	xx			

Note: OR, odds ratio. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest. #, proportional odds assumption is tested using score test.

Table 21. Exploratory analysis of length of stay and health related quality of life outcomes (Intention to treat, unadjusted)

		IO tibial	IO humerus	IV	UNADJUSTED ANALYSIS IO tibial vs IO humerus	UNADJUSTED ANALYSIS IO tibial vs IV MD (95% CI), p value	UNADJUSTED ANALYSIS IO humerus vs IV

					MD (95% CI), p value		MD (95% CI), p value
Critical care length of stay in days (survivors)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Critical care length of stay in days (deceased)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Hospital length of stay in days (survivors)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Hospital length of stay in days (deceased)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L index score at 3 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			

	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L visual analog scale at 3 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L index score at 6 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L visual analog scale at 6 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			

Note: SD, standard deviation. IQR, interquartile range. MD, mean difference. p value adjusted for multiplicity using Bonferroni correction.

Table 22. Exploratory analysis of length of stay and health related quality of life outcomes (Intention to treat, adjusted)

		IO tibial	IO humerus	IV	ADJUSTED ANALYSIS* IO tibial vs IO humerus	ADJUSTED ANALYSIS* IO tibial vs IV	ADJUSTED ANALYSIS* IO humerus vs IV

					MD (95% CI), p value	MD (95% CI), p value	MD (95% CI), p value
Critical care length of stay in days (survivors)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Critical care length of stay in days (deceased)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Hospital length of stay in days (survivors)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
Hospital length of stay in days (deceased)	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L index score at 3 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			

	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L visual analog scale at 3 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L index score at 6 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			
EQ-5D-5L visual analog scale at 6 months	N	xx	xx	xx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx
	Mean	xx	xx	xx			
	Std. Deviation	xx	xx	xx			
	Median	xx	xx	xx			
	IQR	xx - xx	xx - xx	xx - xx			
	Missing	xx	xx	xx			

Note: SD, standard deviation. IQR, interquartile range. MD, mean difference. p value adjusted for multiplicity using Bonferroni correction. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 23. Fragility Index of survival at 30 days (Sensitivity analysis)

		IO (observed)	IV (observed)	Number needed in IO survival to reverse the	Modified IO	UNADJUSTED ANALYSIS*

				statistical significance/non-significance		OR (95% CI), p value
Survival at 30 days	Yes	xx (xx%)	xx (xx%)	xx	xx (xx%)	x.xxx (x.xxx, x.xxx), 0.xxx
	No	xx (xx%)	xx (xx%)		xx (xx%)	
	Missing	xx	xx	xx	xx	

Note: OR, odds ratio.

Table 24. Analysis of imputed survival at 30 days and functional outcomes (Sensitivity analysis)

Outcome	**Imputation method**		**IO**	**IV**	**UNADJUSTED ANALYSIS** **OR (95% CI), p value**
Survival at 30 days	MICE		**NA**	**NA**	x.xxx (x.xxx, x.xxx)
	Best scenario	Yes	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		No	xx (xx%)	xx (xx%)	
	Worst scenario	Yes	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		No	xx (xx%)	xx (xx%)	
	Tipping point	Yes	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		No	xx (xx%)	xx (xx%)	
Modified Rankin Scale at hospital discharge	MICE		**NA**	**NA**	x.xxx (x.xxx, x.xxx)
	Extrapolation/interpolation	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	LVCF/NVCB	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Best scenario	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Worst scenario	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)

		Unfavourable	xx (xx%)	xx (xx%)	
	Tipping point	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
Modified Rankin Scale at 3 months	MICE		**NA**	**NA**	x.xxx (x.xxx, x.xxx)
	Extrapolation/interpolation	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	LVCF/NVCB	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Best scenario	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Worst scenario	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Tipping point analysis	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
Modified Rankin Scale at 6 months	MICE		**NA**	**NA**	x.xxx (x.xxx, x.xxx)
	Extrapolation/interpolation	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	LVCF/NVCB	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Best scenario	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Worst scenario	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	
	Tipping point	Favourable	xx (xx%)	xx (xx%)	x.xxx (x.xxx, x.xxx)
		Unfavourable	xx (xx%)	xx (xx%)	

Note: OR, odds ratio. MICE: multiple imputation by chained equation. Extrapolation/interpolation: missing functional data will be derived using the sequence of collected mRS data at the other follow-ups. LVCF, Last value carried forward/NVCB, next value carried backward: missing functional data will be imputed using the last observed or next observed value, depending on the missing pattern. Best scenario: all missing functional (survival) data will be imputed as favourable (alive) outcome. Worst scenario: all missing functional (survival) data will be imputed as unfavourable (deceased) outcome.

Table 25. Inverse probability of censoring weighted analysis of survival at 30 days (sensitivity analysis)

	UNADJUSTED ANALYSIS OR (95% CI), p value	ADJUSTED ANALYSIS* OR (95% CI), p value
Survival at 30 days	x.x (x.x, x.x), 0.xxx	x.x (x.x, x.x), 0.xxx

Note: IPCW, Inverse probability of censoring weights. OR, odds ratio. p value is not adjusted for interim analyses. *, analysis is adjusted for age, sex, witnessed, bystander CPR, initial rhythm, time from 999 call to drug administration, aetiology of cardiac arrest.

Table 26. Bayesian analysis of survival at 30 days

Survival at 30 days	**Prior**			
IO vs IV	Non-informative Normal (x, x)	Informative Normal (x, x)	Enthusiastic Normal (x, x)	Sceptical Normal (x, x)
Probability of risk difference>0	0.xx	0.xx	0.xx	0.xx
Probability of risk difference>1%	0.xx	0.xx	0.xx	0.xx
Probability of risk difference>2%	0.xx	0.xx	0.xx	0.xx
Probability of risk difference>3%	0.xx	0.xx	0.xx	0.xx

Note: A positive risk difference is interpreted as IO has higher survival rate than IV.