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

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Table of Contents

Plain English Summary

Cardiac arrest occurs when the heart stops beating suddenly. This causes a loss of blood flow to vital organs resulting in unconsciousness and death if treatment is not immediate. Adrenaline is effective in restarting the heart after a cardiac arrest and can be given by injection through the vein or bone marrow. The PARAMEDIC-3 trial compares outcomes in people with out-of-hospital cardiac arrest given adrenaline through the vein (intravenous) and through the bone (intraosseous).

Cost-effectiveness analysis compares the costs and outcomes of alternative treatments. PARAMEDIC-3 investigates whether intraosseous adrenaline administration is a cost-effective alternative to intravenous adrenaline administration. We will collect costs of the treatments and subsequent healthcare received by patients. Patient health-related quality-of-life will be recorded using the EQ-5D-5L questionnaire and, together with patient survival, will be used to calculate Quality-Adjusted Life Years (QALYs).

We will present our findings in terms of the incremental costs per QALY gained using data collected within the trial. We will use a decision analysis model to explore the impact of both interventions on costs and outcomes after the trial ends.

Objective

The aim of the trial health economic evaluation is to estimate the cost-effectiveness of an intraosseous (IO) access first strategy, compared with an intravenous (IV) access first strategy in out-of-hospital cardiac arrest. The evaluation is being conducted alongside the Pre-hospital Randomised Trial of Medication route in out-of- hospital Cardiac arrest (PARAMEDIC-3) trial. PARAMEDIC-3 is a pragmatic, individually randomised, parallel group, superiority trial with an embedded economic evaluation. The health economics analysis plan describes prospectively an explicit framework of methods that will be used to analyse the health economic data.

Background

Cardiac arrest drug treatments are effective in restarting the heart following cardiac arrest [1, 2]. A previous trial (PARAMEDIC-2 trial) showed that parenteral adrenaline, compared with placebo, is highly effective at restarting the heart (adjusted OR 3.83, 95% confidence internal (CI) 3.3-4.43), but has a much smaller effect on long-term survival (OR 1.39, 95% CI 1.06-1.82) and favourable neurological function (1.18, 0.86-1.61). Modelling data from PARAMEDIC-2 shows that every one-minute reduction in time to drug administration from ambulance arrival increases absolute 30-day survival by 0.7% (a 22% relative increase)[3].

Current clinical guidelines recommend that cardiac arrest drugs are administered through the intravenous (IV) route, wherever possible [4]. However, peripheral IV cannulation is very challenging during out-of-hospital cardiac arrest due to both patient (e.g., veins collapsed) and environmental (e.g., sub-optimal positioning, poor lighting) issues. IV vascular access is successfully achieved at the first attempt in only around 50% of cases.[5] Repeated attempts at IV cannulation delay time to drug administration and distract the limited resuscitation team from other key tasks.

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[6] and an overall reduction in survival[7, 8]. The PARAMEDIC-3 trial aims to establish whether the use of an IO access first strategy is both a clinically and cost-effective alternative to an IV access first strategy in out-of-hospital cardiac arrest.

General Principles for economic evaluation

The within-trial economic analysis will be conducted according to intention to treat (ITT) principles[9]. The perspective of the base case analysis will be that of the UK health and personal social care services (NHS/PSS) as recommended by National Institute for Health and Care Excellence (NICE) reference case for appraising health technologies [10]. Secondary analyses will consider costs from a wider societal perspective [11]. A 6-month time horizon will be adopted to match the trial follow-up period covering the 6 months period following out-of-hospital cardiac arrest. As a result, no discounting will be applied to costs and outcomes in the within-trial analysis. However, if longer term decision modelling were to be undertaken, then costs and outcomes will be discounted at 3.5% beyond the first year post randomisation in accordance with the NICE reference case [10]. The findings of this economic evaluation will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of health economic evaluations [12].

Resource use and costs

Data will be collected on the health and social service use and costs for each trial participant during the period between randomisation and six months post-randomisation. Resource utilisation data will be collected through: (i) use of trial interventions, concurrent treatments, mode and distance of initial transportation and subsequent transfers, with these estimated using the computerised data collection systems developed for the PARAMEDIC-3 trial; (ii) detailed information on ITU resource utilisation and specific treatments (e.g. cardiovascular support) will be collected using bespoke trial data collection forms; this information will in turn be validated, and where necessary complemented, using information collected from the Intensive Care Research National Audit Programme (ICNARC); (iii) the National Cardiovascular Outcomes Research (NICOR) datasets; iv) information on subsequent hospital inpatient and day case admissions and outpatient visits will be collected though Hospital Episode Statistics; and (v) trial participants or, where necessary, appropriate proxies will be asked to complete economic questionnaires profiling hospital readmissions and post-discharge health and social community care resource use at each time point of follow-up. A sensitivity analysis will replicate the economic evaluation from a societal perspective: out-of-pocket expenses, and costs associated with lost productivity will also be measured in the economic questionnaires.

Resource units in each trial arm will be valued using UK national tariffs. Unit costs for community care services will be valued using Personnel and Social Services Unit costs compendium[13] A per diem cost for each level of outpatient and in-patient hospital care, delineated by level of intensity will be valued using NHS reference costs[14]. Medication will be costed using the Prescription Cost Analysis (PCA)[15]. Personal and social services used will valued using the PSSRU[13]. Aids and adaptation received will be valued using prices from the NHS supply chain catalogue. Costs due to lost productivity will be valued using published national average weekly earnings[16].

The primary analysis will concentrate on direct intervention and healthcare/PSS costs, whilst broader societal costs will be included in a sensitivity analysis.

Outcomes

In accordance with NICE guidelines, the primary outcome for the within-trial analysis is the quality adjusted life years (QALYs) measure[17]. The QALY combines quantity (time) and health-related quality of life into a single metric using an area-under-the-curve calculation [18]. Health related quality of life data will be collected from trial participants using the EuroQol EQ-5D-5L[19] at hospital discharge or 30 days post-OHCA, 3- and 6-months post-randomisation, and converted into health state utilities. The EQ-5D-5L is a generic preference based five-dimensional multi-attribute instrument for measuring health-related quality of life. There are two versions of the questionnaire: the 3-level and 5-level version. Patients in PARAMEDIC-3 will complete the 5-level version. Where a patient lacks capacity to complete a questionnaire, appropriate proxies will be asked to complete the questionnaire. Secondary health economic outcomes to be considered will include: (i) incremental cost per additional survivor to 30 days post-cardiac arrest, (ii) incremental costs per additional survivor to hospital discharge and (iii) incremental cost per additional neurologically unimpaired (mRS score) survivor at hospital discharge.

Obtaining baseline quality of life data in critical illness settings can be challenging as patients are normally incapacitated or unable to complete patient reported questionnaires at time of randomisation [20]. Baseline health-related quality of life immediately following OHCA will be assumed to be equivalent to the worst health state in the EQ-5D-5L in the EQ-5D-3L value set (-0.59)[21].

Responses to the EQ-5D-5L questionnaires will be converted into utility scores using established algorithms. The method recommended by NICE at the time of analysis will be applied [22]: currently this involves mapping to the EQ-5D-3L using the 'cross-walk' developed by van Hout et al[23]. Utility values will be re-evaluated using alternative mapping algorithms[24]. Utility values derived from the EQ-5D-3L will be used for the base case analysis.

Missing data

Missing data is a common occurrence within RCTs, and all missing data will be handled in a principled manner. Descriptive analysis of the missing data will be carried out, the results of which will inform assumptions about the missing data mechanism. In line with best practice, the base case analysis will use multiple imputation to account for missing data (rather than a complete case analysis), assuming overall missingness exceeds 5%. The base case analysis will present the imputed within trial incremental cost and QALYs gained, adjusted for trial covariates. Supportive sensitivity analyses will include participants with complete data and explore the impact of imputation.

Imputation will be conducted according to good practice guidance [25]. Multiple imputation provides unbiased estimates of treatment effect if data are missing at random: this assumption will be explored in the data, for example by using logistic regression for missingness of costs and QALYs against baseline variables [26]. A regression model will be used to generate multiple imputed datasets (or 'draws') for individual treatment groups, where missing values are predicted. Outcome measures and costs (at each time point) will contribute as predictors and imputed variables. Trial stratification variables will be included as predictors in the imputation. Each draw provides a complete dataset, which reflects the distributions and correlations between variables. Predictive mean matching drawn from the five nearest neighbours (knn=5) will be used to enhance the plausibility and robustness of imputed values, as normality may not be assumed. The imputation model will use fully conditional (MICE) methods (multiple imputation by chained equations), which are appropriate when missing and correlated data occur in more than one variable. Each draw will be analysed independently using bivariate regression (see below) and the estimates obtained will be pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule – a method that captures within and between variances for imputed samples [27]. To minimise the information loss of finite imputation sampling, a minimum of 20 draws will be taken. The distribution of imputed and observed values will be compared visually and statistically to establish the consequences of estimation.

Cost-effectiveness analysis

Bivariate regression using seemingly unrelated regression equations will be used to model incremental costs and QALYs. This method respects the correlation of costs and outcomes within the data, and allows adjustment for a set of covariates, which can be explored and which improve precision [28]. Baseline QoL scores will be included within all models to allow for potential baseline imbalances [29]. Failure to account for baseline imbalances may lead to biased cost-effectiveness estimates. Joint distributions of costs and outcomes will be generated using the (non-parametric) bootstrap method, with replicates used to populate the cost-effectiveness plane. Bootstrapping jointly resamples costs and outcomes from the original data with replacement (maintaining the sample correlation structure) to create a new bootstrap sample from which a change in costs and QALYs are estimated. Using non-parametric bootstrapping, 2000 bootstraps will be taken per model evaluated. Mean estimates will be reported with 95% confidence regions.

The incremental cost-effectiveness ratio (ICER) will be estimated as the difference between treatments in average total costs divided by the difference in average total QALYs. Value-for-money is determined by comparing the ICER with a threshold value, typically the NICE threshold for British studies, of £20k-30k/QALY[17]. This represents the willingness to pay for an additional QALY, and lower values than the threshold could be considered cost-effective for use in the NHS. Base case assumptions will be explored using a range of supportive sensitivity analyses, providing an assessment of the robustness of findings.

The net monetary benefit (NMB) of adopting the new treatment will be reported as a recalculation of the ICER at a range of thresholds of willingness to pay for an additional QALY. The NMB succinctly describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at (up to) the same threshold. NMB estimates will be

used to generate cost-effectiveness acceptability curves (CEACs). The CEAC compares the likelihood that treatments are cost-effective as the willingness to pay threshold varies [13].

We will construct a decision-analytical model to extrapolate beyond the proposed trial period to explore the long-term cost-effectiveness of IO access first strategy vs IV access first strategy in this clinical population. Survival analysis models will be used to estimate life expectancy in both trial groups beyond the time horizon of the trial. Long term estimates of costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom. Using a decision analytic model, we will also explore the impact of organ recovery on the cost-effectiveness analysis. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios.

Pre-specified sub-group analysis

These would include all subgroup analysis pre-specified in the statistical analysis plan that are appropriate to be undertaken for the economic endpoints of interest.

- Age (≤ 60 years vs > 60 years)
- Cardiac arrest witnessed by bystander versus not witnessed by bystander
- Bystander CPR versus no bystander CPR
- Aetiology of cardiac arrest (presumed cardiac versus non-cardiac).
- Type of initial rhythm (shockable (VT/VF) versus non-shockable (PEA/Asystole)
- Time interval of 999 call to emergency medical services (EMS) arrival (≤ 10 minutes vs > 10 minutes).
- Time interval of EMS arrival to drug administration (≤ 10 minutes vs > 10 minutes).
- Time interval from 999 call to drug administration (≤ 10 minutes vs > 10 minutes)

Pre-specified exploratory subgroup analyses will be analysed using interaction term (treatment x sub-group) in the statistical models and reported using 95% confidence intervals, as the trial is not powered to identify interactions.

Results table

Table 1 Completion rates for health economic outcomes

	Completion rates		
Assessment point and resource category	IO (n=xxx)	IV (n=xxx)	Total
Post-OHCA[1]			
EQ-5D-5L index	xxx%	xxx%	xxx%
EQ-5D-5L VAS	xxx%	xxx%	xxx%
ROSC			
Return of spontaneous circulation (ROSC) > 20 minutes	xxx%	xxx%	xxx%
3 *months' assessment point*			
Time spent in hospital immediately following cardiac arrest	xxx%	xxx%	xxx%
Use of hospital based or residential care services since being discharged from hospital following cardiac arrest	xxx%	xxx%	xxx%
Use of community based health and social services since cardiac arrest. this includes any services that are not within the hospital for example, visits to the GP)	xxx%	xxx%	xxx%
Medication use	xxx%	xxx%	xxx%
Special equipment or aids	xxx%	xxx%	xxx%
Time off work	xxx%	xxx%	xxx%
EQ-5D-5L index	xxx%	xxx%	xxx%
EQ-5D-5L VAS	xxx%	xxx%	xxx%
6 month months' assessment point			
Time spent in hospital immediately following cardiac arrest	xxx%	xxx%	xxx%
Use of hospital based or residential care services since being discharged from hospital following cardiac arrest	xxx%	xxx%	xxx%
Use of community based health and social services since cardiac arrest. this includes any services that are not within the hospital for example, visits to the GP)	xxx%	xxx%	xxx%
Medication use	xxx%	xxx%	xxx%
Special equipment or aids	xxx%	xxx%	xxx%
Time off work	xxx%	xxx%	xxx%
EQ-5D-5L index	xxx%	xxx%	xxx%
EQ-5D-5L VAS	xxx%	xxx%	xxx%

[1] response solicited at either hospital discharge or 30 days after cardiac arrest.

Table 2 Patient and proxy reported of health and social care utilisation during trial follow-up

		IO(n=xxxx)			IV (n=xxxx)			IO versus IV	
Assessment point	Category	% missing	Number of visits, mean (sd)	Total number of days, mean (sd)	% missing	Number of visits, mean (sd)	Total number of days, mean (sd)	Mean difference, [1]	P-value
0 to 3 months post randomisation	*Inpatient stay immediately following arrest*								
	Intensive care unit								
	Cardiac care unit								
	General ward								
	Inpatient stay since being discharged from hospital								
	Hospital outpatient clinic								
	Cardiology								
	Surgery								
	Hospital accident and emergency department								
	Nursing/residential home								
	Community health and social care								
	GP, surgery visit								
	GP, home visit								
	District nurse/Health visitor								
	Practice nurse								
	Occupational therapist								
	Counsellor								
	Calls to NHS 111								
	Calls to ambulance or paramedic								
	Speech and language therapist								
	Mental health services								

	Food, medicine or laundry delivery service								
	Social worker contacts								
	Medication use								
	Special equipment and aids								
4-6 months post randomisation	*Inpatient stay immediately following arrest*								
	Intensive care unit								
	Cardiac care unit								
	General ward								
	Inpatient stay since being discharged from hospital								
	Hospital outpatient clinic								
	Cardiology								
	Surgery								
	Other hospital/residential care								
	Hospital accident and emergency department								
	Nursing/residential home								
	Other hospital/residential care								
	Community health and social care								
	GP, surgery visit								
	GP, home visit								
	District nurse/Health visitor								
	Practice nurse								
	Occupational therapist								
	Counsellor								
	Calls to NHS 111								
	Calls to ambulance or paramedic								
	Speech and language therapist								

	Mental health services								
	Food, medicine or laundry delivery service								
	Social worker contacts								
	Medication use								
	Special equipment and aids								

[1]mean difference and 95% CIs for total number of days or number of contacts/visits when number of days is not relevant

Table 3 Patient and proxy reported of health and social care costs during trial follow-up

		IO (n=xxxx)	IV (n=xxxx)	IO versus IV	
Assessment point	Category	Mean cost (sd)	Mean cost (sd)	Mean difference[1]	P-value
0 to 3 months post randomisation	*Inpatient stay immediately following arrest*				
	Intensive care unit				
	Cardiac care unit				
	General ward				
	Inpatient stay since being discharged from hospital				
	Total inpatient costs				
	Hospital outpatient clinic				
	Cardiology				
	Surgery				
	Hospital accident and emergency department				
	Nursing/residential home				
	Total outpatient costs				
	Community health and social care				
	GP, surgery visit				
	GP, home visit				
	District nurse/Health visitor				
	Practice nurse				
	Occupational therapist				
	Counsellor				
	Calls to NHS 111				
	Calls to ambulance or paramedic				
	Speech and language therapist				

	Mental health services				
	Food, medicine or laundry delivery service				
	Medication use				
	Special equipment and aids				
	Total other healthcare costs				
	Total cost from 0-3 months				
4 to 6 months post randomisation	*Inpatient stay immediately following arrest*				
	Intensive care unit				
	Cardiac care unit				
	General ward				
	Inpatient stay since being discharged from hospital				
	Total inpatient costs				
	Hospital outpatient clinic				
	Cardiology				
	Surgery				
	Hospital accident and emergency department				
	Nursing/residential home				
	Total outpatient costs				
	Community health and social care				
	GP, surgery visit				
	GP, home visit				
	District nurse/Health visitor				
	Practice nurse				
	Occupational therapist				
	Counsellor				
	Calls to NHS 111				

	Calls to ambulance or paramedic			
	Speech and language therapist			
	Mental health services			
	Food, medicine or laundry delivery service			
	Medication use			
	Special equipment and aids			
	Total other healthcare costs			
	Total cost from 4-6 months			

Table 4 Total economic costs

Costing perspective and list of included cost categories	IO (n=xxxx)	IV (n=xxxx)	IO versus IV	
	Mean (SE), £	Mean (SE), £	Mean difference (bootstrap 95% CI[1]), £	P-value[2]
NHS/PSS perspective				
Treatment costs				
Follow-up costs				
Total NHS/PSS costs				
Societal perspective				
Treatment costs				
Follow-up costs (NHS/PSS)				
Follow-up costs (non-NHS/PSS)				
Total societal costs				

[1]Confidence intervals obtained by bootstrap percentile method [2]Two-sided p-values obtained by counting the proportion of bootstrap replicates in which the mean cost-difference is positive, multiplied by 2 and take a minimum

Table 5 Summary of health-related quality of life (utility) scores generated from the EQ-5D-5L instrument

Outcomes	IO		IV		IO versus IV	
	N	Mean (SE)	N	Mean (SE)	Mean difference (95% CI)	P-value
EQ-5D-5L to 3L cross walk[1]						
Post-OHCA[2]	xxxx		xxxx			
3 months	xxxx		xxxx			
6 months	xxxx		xxxx			
EQ-5D-5L VAS						
Post-OHCA[2]	xxxx		xxxx			
3 months	xxxx		xxxx			
6 months	xxxx		xxxx			

[1]The EQ-5D-5L cross-walk utility values were derived using the interim 5L to 3L cross-walk tariffs for the UK [23]
[2]Post-OHCA health-related quality of life was collected using the EQ-5D-5L at discharge or 30 days following OHCA

Table 6 Unadjusted estimates of Quality-Adjusted Life Years (QALYs) accrued over 6 months of follow-up

Outcome measure	IO		IV		IO versus IV	
	N	Mean (SE)	N	Mean (SE)	Mean difference (95% CI)	P-value
EQ-5D-5L cross-walk tariff	xxxx		xxxx			

Table 7 Cost-effectiveness results for the within-trial economic analysis

	Cost-effectiveness outcomes				Probability IO is cost-effective at cost-effectiveness threshold of		
Description	Mean incremental costs (95% CI), £	Mean incremental QALYs (95% CI)	ICER[4]		£15,000 per QALY	£20,000 per QALY	£30,000 per QALY
Base case analysis[1]							
Sensitivity analyses							
Complete case analysis							
Survival to 30 days post-cardiac arrest							
Survival to hospital discharged							

Neurologically unimpaired survivor (mRS) at hospital discharge							
Sub-groups							
Cardiac arrest witnessed by Crew/public bystander Not witnessed							
Bystander CPR Yes No							
Type of initial rhythm VT/VF PEA/Asystole							
Aetiology of cardiac arrest Presumed cardiac medical Non-cardiac medical							
Time from 999 call to administration of trial drug Time category 1 Time category 2							
Time interval from EMS arrival to administration of trial drug							
≤10 minutes							
>10 minutes							
Time interval from EMS arrival to administration of trial drug							
≤10 minutes							
>10 minutes							
Age ≤60 years >60 years							

ICER = Incremental cost-effectiveness ratio; CI = confidence interval

[1]Adjusted for treatment allocation, age, sex, time to 1st dose administration, witness, bystander CPR, initial aetiology, initial rhythm and total drug dose, baseline health-related quality of life

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