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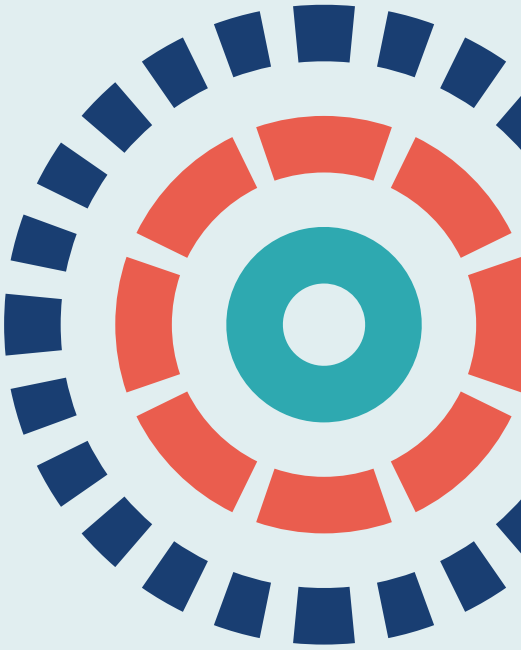

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Adrenaline to improve survival in out-of-hospital cardiac arrest: the PARAMEDIC2 RCT

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This report

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Abstract

Adrenaline to improve survival in out-of-hospital cardiac arrest: the PARAMEDIC2 RCT

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Background: Adrenaline has been used as a treatment for cardiac arrest for many years, despite uncertainty about its effects on long-term outcomes and concerns that it may cause worse neurological outcomes.

Objectives: The objectives were to evaluate the effects of adrenaline on survival and neurological outcomes, and to assess the cost-effectiveness of adrenaline use.

Design: This was a pragmatic, randomised, allocation-concealed, placebo-controlled, parallel-group superiority trial and economic evaluation. Costs are expressed in Great British pounds and reported in 2016/17 prices.

Setting: This trial was set in five NHS ambulance services in England and Wales.

Participants: Adults treated for an out-of-hospital cardiac arrest were included. Patients were ineligible if they were pregnant, if they were aged < 16 years, if the cardiac arrest had been caused by anaphylaxis or life-threatening asthma, or if adrenaline had already been given.

Interventions: Participants were randomised to either adrenaline (1 mg) or placebo in a 1 : 1 allocation ratio by the opening of allocation-concealed treatment packs.

Main outcome measures: The primary outcome was survival to 30 days. The secondary outcomes were survival to hospital admission, survival to hospital discharge, survival at 3, 6 and 12 months, neurological outcomes and health-related quality of life through to 6 months. The economic evaluation assessed the incremental cost per quality-adjusted life-year gained from the perspective of the NHS and Personal Social Services. Participants, clinical teams and those assessing patient outcomes were masked to the treatment allocation.

Results: From December 2014 to October 2017, 8014 participants were assigned to the adrenaline ($n = 4015$) or to the placebo ($n = 3999$) arm. At 30 days, 130 out of 4012 participants (3.2%) in the adrenaline arm and 94 out of 3995 (2.4%) in the placebo arm were alive (adjusted odds ratio for survival 1.47, 95% confidence interval 1.09 to 1.97). For secondary outcomes, survival to hospital admission was higher for those receiving adrenaline than for those receiving placebo (23.6% vs. 8.0%; adjusted odds ratio 3.83, 95% confidence interval 3.30 to 4.43). The rate of favourable neurological outcome at hospital discharge was not significantly different between the arms (2.2% vs. 1.9%; adjusted odds ratio 1.19, 95% confidence interval 0.85 to 1.68). The pattern of improved survival but no significant improvement in neurological outcomes continued through to 6 months. By 12 months, survival in the adrenaline arm was 2.7%, compared with 2.0% in the placebo arm (adjusted odds ratio 1.38, 95% confidence interval 1.00 to 1.92). An adjusted subgroup analysis did not identify significant interactions. The incremental cost-effectiveness ratio for adrenaline was estimated at £1,693,003 per quality-adjusted life-year gained over the first 6 months after the cardiac arrest event and £81,070 per quality-adjusted life-year gained over the lifetime of survivors. Additional economic analyses estimated incremental cost-effectiveness ratios for adrenaline at £982,880 per percentage point increase in overall survival and £377,232 per percentage point increase in neurological outcomes over the first 6 months after the cardiac arrest.

Limitations: The estimate for survival with a favourable neurological outcome is imprecise because of the small numbers of patients surviving with a good outcome.

Conclusions: Adrenaline improved long-term survival, but there was no evidence that it significantly improved neurological outcomes. The incremental cost-effectiveness ratio per quality-adjusted life-year exceeds the threshold of £20,000–30,000 per quality-adjusted life-year usually supported by the NHS.

Future work: Further research is required to better understand patients' preferences in relation to survival and neurological outcomes after out-of-hospital cardiac arrest and to aid interpretation of the trial findings from a patient and public perspective.

Trial registration: Current Controlled Trials ISRCTN73485024 and EudraCT 2014-000792-11.

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List of abbreviations

AED	automated external defibrillator
ALS	advanced life support
aOR	adjusted odds ratio
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
CRF	case report form
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
EFIC	exception from informed consent
EMS	emergency medical services
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GCP	good clinical practice
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICNARC	Intensive Care National Audit and Research Centre
ICU	intensive care unit
ILCOR	International Liaison Committee on Resuscitation
IMP	Investigational Medicinal Product
INMB	incremental net monetary benefit
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	interquartile range
i.v.	intravenous
JRCALC	Joint Royal Colleges Ambulance Liaison Committee
LTFU	lost to follow-up
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	multiple imputation by chained equations
MMSE	Mini Mental State Examination
mRS	modified Rankin Scale
NICE	National Institute for Health and Care Excellence
OHCA	out-of-hospital cardiac arrest
OHCAO	Out-of-Hospital Cardiac Arrest Outcomes
OR	odds ratio
PACA	Pre-hospital Adrenaline for Cardiac Arrest

PAD	public access defibrillation
PaRAMeDIC	Prehospital Randomised Assessment of a Mechanical compression Device In Cardiac arrest
PARAMEDIC2	Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest 2
PCL-C	Post-traumatic stress disorder Checklist – Civilian Version
PEA	pulseless electrical activity
PEDW	Patient Episode Database for Wales
PPI	patient and public involvement
PSS	Personal Social Services
PTSD	post-traumatic stress disorder
QALY	quality-adjusted life-year
REC	Research Ethics Committee
RFA	Rankin Focused Assessment
ROC	Resuscitation Outcomes Consortium
ROSC	return of spontaneous circulation
RR	risk ratio
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-12	Short Form questionnaire-12 items
smRSq	simplified modified Rankin Scale questionnaire
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UKTR	UK Transplant Registry
VF	ventricular fibrillation
VT	ventricular tachycardia
WCTU	Warwick Clinical Trials Unit

Plain English summary

Cardiac arrest is a medical emergency that happens when the heart suddenly stops pumping effectively. When cardiac arrest happens, awareness is lost within seconds. If emergency treatment is not started quickly, the person will die. The first treatments of cardiac arrest involve pressing on the chest, giving rescue breaths and defibrillation (electric shocks applied to the heart). If these treatments do not work, ambulance paramedics use a drug called adrenaline to try to restart the heart. Although this treatment has been used for many years, some recent research suggests that it may cause more harm than good.

In this research study, we compared the effects of giving adrenaline with the effects of not giving adrenaline to people who had a cardiac arrest in the community. The research showed that adrenaline was effective at restarting the heart, so more people survived long enough to be admitted to hospital. Thirty days later, 130 out of 4012 patients (3.2%) who received adrenaline and 94 out of 3995 (2.4%) who did not receive adrenaline were alive. However, adrenaline did not improve the number of patients who went home from hospital having made a good recovery and were able to care for themselves. The evidence suggests that adrenaline represents a poor use of NHS funds on cost-effectiveness grounds.

In a community survey, 95% of people who responded thought that long-term survival with good brain function was more important than just being alive. Further research exploring the opinions of patients and the public will help to understand the results of this research for the NHS.

Scientific summary

Background

Each year, the NHS treats ≈ 30,000 people who are experiencing out-of-hospital cardiac arrest. Overall survival rates are low (< 10%), falling further (to ≈ 3%) among patients who are unresponsive to initial treatments; such patients require treatment escalation to the use of drugs. Adrenaline has been used as a treatment for cardiac arrest for decades. The International Liaison Committee on Resuscitation examined the evidence for the use of adrenaline in cardiac arrest and identified uncertainty about the effects on long-term outcomes. Some recent, large, observational studies showed a pattern of worse neurological outcomes in patients who received adrenaline. These findings prompted an international call for a trial to examine the clinical effectiveness and safety of adrenaline as a treatment for out-of-hospital cardiac arrest.

Objectives

The primary objective of this trial was to determine the clinical effectiveness of adrenaline in the treatment of out-of-hospital cardiac arrest, measured as 30-day survival (i.e. the primary outcome). The secondary objectives of the trial were to evaluate the effects of adrenaline on survival, neurological outcomes and health-related quality of life among survivors, and to estimate the cost-effectiveness of adrenaline use.

Methods

Ethics and regulatory approvals

The trial was approved by the South Central Oxford C Research Ethics Committee (reference number 14/SC/0157) and the Medicines and Healthcare Products Regulatory Agency (EudraCT number 2014-000792-11). The trial was sponsored by the University of Warwick and was conducted in accordance with the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 [European Commission. *Clinical Trials – Directive 2001/20/EC*. URL: https://ec.europa.eu/health/human-use/clinical-trials/directive_en (accessed 23 September 2020)], The Medicines for Human Use Act (Clinical Trial) Regulations, Statutory Instrument 2004 No. 1031 and Amendment (No.2) Statutory Instrument 2006 No. 2984 [Great Britain. *The Medicines for Human Use (Clinical Trials) Regulations 2004*. London: The Stationery Office; 2004 (and amendment in 2006)].

The Confidentiality Advisory Group provided approval under regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 [Great Britain. *The Health Service (Control of Patient Information) Regulations 2002*. London: The Stationery Office; 2002] to process patient-identifiable information without consent (reference number 14/CAG/1009).

Design

This was a pragmatic, randomised, allocation-concealed, placebo-controlled, parallel-group superiority trial and economic evaluation.

Inclusion and exclusion criteria

Patients were eligible if both of the following criteria were met:

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

Exclusion criteria at the time of arrest were as follows:

- known or apparent pregnancy
- known to be or apparently aged < 16 years
- cardiac arrest caused by anaphylaxis or life-threatening asthma
- adrenaline given prior to arrival of ambulance service clinician.

In London Ambulance Service, traumatic cardiac arrests were also excluded, in accordance with local protocols.

Setting

Recruitment was undertaken in five NHS ambulance services in the UK (London Ambulance Service NHS Trust, North East Ambulance Service NHS Foundation Trust, South Central Ambulance Service NHS Foundation Trust, West Midlands Ambulance Service University NHS Foundation Trust and Welsh Ambulance Service NHS Trust). These ambulance services serve a mix of urban and rural locations in England and Wales, covering a population of 24 million people.

Consent

Cardiac arrest leads to an immediate loss of mental capacity, so it was not possible to obtain informed consent from patients prior to enrolment. The time-critical nature of administering treatments for cardiac arrest meant that it was not practical to obtain informed consent from a personal or professional legal representative without the potential for causing harm through delaying patient treatment. In accordance with the European Union Clinical Trials Directive and the Statutory Instrument 2004/1031, we sought and obtained permission from a Research Ethics Committee to enrol patients prior to obtaining informed consent. Research staff sought written, informed consent from the patient or a legal representative for them to continue in the trial after the initial emergency had passed.

Resuscitation protocols and randomisation process

The NHS ambulance services followed the Joint Royal Colleges Ambulance Liaison Committee guidelines, which are based on the Resuscitation Council (UK) National Institute for Health and Care Excellence-accredited guidelines. The guidelines recommend that initial attempts at resuscitation should comprise initiation of cardiopulmonary resuscitation (chest compressions and ventilations) and defibrillation when indicated. For patients with non-shockable initial rhythms, adrenaline is recommended as soon as vascular access is obtained. For those with shockable initial rhythms, adrenaline is delayed until after the third shock is administered, if the patient remains in cardiac arrest.

The Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest 2 (PARAMEDIC2) trial followed these guidelines. If a patient reached the point in the resuscitation protocol whereby adrenaline was indicated, they were randomly assigned to receive either parenteral adrenaline or saline placebo by the opening of a trial drug pack. Randomisation took place when a trial-trained paramedic opened an Investigational Medicinal Product pack that contained either 10 syringes of adrenaline (1 mg each) or matching placebo (0.9% saline). Patients were randomised to either adrenaline (intervention) or placebo (control) in a 1 : 1 allocation ratio. The adrenaline and placebo packs and syringes were identical in appearance; hence, clinicians, patients and trial personnel did not know whether any specific pack contained adrenaline or placebo.

Single doses of adrenaline or saline were administered every 3–5 minutes by an intravenous or intraosseous route. Clinicians were instructed to use only one treatment pack per patient (10 × 3-ml syringes). Treatments were continued until a sustained pulse was achieved, resuscitation was discontinued or care was handed over to a clinician at the receiving hospital.

Outcomes

The primary outcome was survival to 30 days.

The secondary outcomes were as follows:

- survived event (sustained return of spontaneous circulation, with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital)
- survival to hospital discharge (the point at which the patient is discharged from the hospital acute care unit, regardless of neurological status, outcome or destination) and to 3, 6 and 12 months
- neurological outcome (measured using the modified Rankin Scale) at hospital discharge and at 3 and 6 months (assessed at discharge using the Rankin Focused Assessment), and completed at 3 and 6 months via the simplified modified Rankin Scale questionnaire
- neurological outcomes (measured using the Informant Questionnaire on Cognitive Decline in the Elderly and 'Two Simple Questions') at 3 and 6 months
- health-related quality of life at 3 and 6 months (measured using the Short Form questionnaire-12 items and the EuroQol-5 Dimensions, five-level version)
- cognitive outcome at 3 months (measured using the Mini Mental State Examination)
- anxiety and depression at 3 months (measured using the Hospital Anxiety and Depression Scale)
- post-traumatic stress at 3 months (measured using the Post-traumatic stress disorder Checklist-Civilian version)
- hospital length of stay
- intensive care unit length of stay.

Economic evaluation

The primary economic evaluation was the incremental cost per quality-adjusted life-year gained from the perspective of the NHS and Personal Social Services.

The secondary economic evaluation considered the cost of critical care stay (level 2/3 days), the cost of hospital stay, utilisation of NHS and Personal Social Services resources after discharge and broader resource utilisation after discharge.

Data were collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 6 months post randomisation.

An incremental cost-effectiveness analysis was performed, and results were presented using incremental cost-effectiveness ratios and cost-effectiveness acceptability curves, generated via seemingly unrelated linear regressions and non-parametric bootstrapping. A decision-analytic model was used to extrapolate economic outcomes beyond the trial-follow-up and to assess the cost-effectiveness of adrenaline over the lifetimes of cardiac arrest survivors. Long-term costs and health consequences were reduced to present values using discount rates recommended for health technology appraisal in the UK. A series of probabilistic sensitivity analyses were undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios.

Sample size and statistical analysis

The target sample size was 8000 participants, which was expected to give a width of the 95% confidence interval for the risk ratio of approximately 0.4 or slightly less; for a risk ratio of 1.25, the 95% confidence interval was 1.07 to 1.46, and for a risk ratio of 1.0, it was 0.84 to 1.19. During the conduct of the trial, the event rate for the primary outcomes was observed to be lower than that

originally expected. Modelling various scenarios, and noting that an absolute risk reduction of 1% had been used widely in resuscitation trials to define the minimal clinically important difference, it was concluded that the trial would still yield valuable information about the safety and clinical effectiveness of adrenaline if the observed survival rates continued to the end of the trial.

The primary analysis was performed with and without adjustment in the modified intention-to-treat population, which included all the patients who had undergone randomisation and were confirmed to have received the assigned intervention. Fixed-effect regression models were used to examine survival outcomes with and without adjustment. Variables included in adjusted analyses were age, sex, the time between the 999 call and the ambulance arriving at the scene, the time between the ambulance arriving and trial drug administration, the suspected aetiology of the cardiac arrest, the initial heart rhythm, whether or not the event was witnessed, and whether or not a bystander undertook cardiopulmonary resuscitation.

The Hodges–Lehmann method was used to estimate median differences with 95% confidence intervals for length-of-stay outcomes. In cases in which the proportional odds assumption was violated in modelling of the score on the modified Rankin Scale, partial proportional odds models were used. Scores on the modified Rankin Scale were also analysed as a binary outcome (with scores of 0–3 classified as 'good' and scores of 4–6 classified as 'poor'). Other secondary outcomes (including quality of life and neurological and cognitive functions) were summarised by treatment arm. To aid in interpretation, we included a Bayesian analysis for the primary outcome and for survival with a favourable neurological outcome.

Patient and public involvement

A community engagement event was held prior to the start of the trial to assess the need and acceptability of the trial and to explore which outcomes were most important to patients. Information about the trial was disseminated through both health-care and non-health-care settings. Throughout the trial, we met regularly with patient and public groups, including a patient and public advisory group. A lay member of the trial team and two independent patient and public representatives served on the Trial Management Committee and Trial Steering Committee, respectively.

Results

From December 2014 to October 2017, 8014 patients were assigned either to the adrenaline arm ($n = 4015$) or to the placebo arm ($n = 3999$). At 30 days, 130 out of 4012 patients (3.2%) in the adrenaline arm and 94 out of 3995 patients (2.4%) in the placebo group were arm (adjusted odds ratio for survival 1.47, 95% confidence interval 1.09 to 1.97). For secondary outcomes, a larger proportion of participants in the adrenaline arm than in the placebo arm survived to hospital admission (23.6% vs. 8.0%; adjusted odds ratio 3.83, 95% confidence interval 3.30 to 4.43). The rate of favourable neurological outcome at hospital discharge was not significantly different between the arms (2.2% in the adrenaline arm vs. 1.9% in the placebo arm; adjusted odds ratio 1.19, 95% confidence interval 0.85 to 1.68). The pattern of improved survival, but no significant improvement in neurological outcomes, continued to 6 months. By 12 months, survival in the adrenaline arm was 2.7%, compared with 2.0% in the placebo arm (adjusted odds ratio 1.38, 95% confidence interval 1.00 to 1.92). A Bayesian analysis found a 37% probability that the absolute rate of survival was > 1% in the adrenaline arm and a 1.9% probability for a > 1% improvement in favourable neurological outcome. An adjusted subgroup analysis did not identify any significant interactions.

Severe neurological impairment (a score of 4 or 5 on the modified Rankin Scale) at discharge was more common among survivors in the adrenaline arm than among those in the placebo arm [39/126 (31.0%) vs. 16/90 (17.8%) patients, respectively]. The number of patients with severe neurological impairment decreased through to 6 months, although evaluation was limited by greater loss to follow-up.

Examining health-related quality of life up to 6 months after randomisation and examining cognitive function, anxiety/depression or post-traumatic stress to 3 months showed that there was significant functional impairment in cardiac arrest survivors, compared with the normal population. One-third to half of patients reported that they needed help from someone with everyday activities. For most, this was a new situation after their cardiac arrest. Fewer than half reported having made a full mental recovery after their cardiac arrest. Although underpowered, the pattern of impairment suggested greater disability in the adrenaline group.

The incremental cost-effectiveness ratio for adrenaline was estimated at £1,693,003 per quality-adjusted life-year gained over the first 6 months after the cardiac arrest event, and £81,070 per quality-adjusted life-year gained over the lifetime of survivors. The associated adjusted mean incremental net monetary benefit of adrenaline at cost-effectiveness thresholds of £30,000 per quality-adjusted life-year was −£1282 (95% confidence interval −£1733 to −£831) at 6 months and −£1118 (95% confidence interval −£2776 to £487) over the lifetime of survivors.

Conclusions

Findings from this research indicate that adrenaline was effective at restarting the heart and sustaining circulation to hospital admission following out-of-hospital cardiac arrest. Adrenaline also improved long-term survival, but did not improve survival with favourable neurological outcome. The incremental cost-effectiveness ratio per quality-adjusted life-year exceeds the level usually supported by the NHS.

Further research is required to better understand patients' preferences in relation to survival and neurological outcome after out-of-hospital cardiac arrest and to aid interpretation of the trial findings from a patient and public perspective. Further research examining the time to adrenaline administration and the route of administration (intravenous or intraosseous) may provide additional insights to the trial's findings.

Trial registration

This trial is registered as ISRCTN73485024 and EudraCT 2014-000792-11.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 25. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Description of condition

Out-of-hospital cardiac arrest (OHCA) is defined as the loss of functional cardiac mechanical activity, in association with an absence of systemic circulation, occurring outside a hospital setting.[1]

The majority of OHCA events result from cardiac causes such as ischaemic heart disease, myocardial infarction and rhythm disturbances. Other causes of OHCA include trauma, submersion, drug overdose, asphyxia, exsanguination or other medical causes such as stroke or pulmonary embolism.[2,3]

Cardiac arrest occurs through three different mechanisms: (1) lethal arrhythmias [ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)] leading to loss of cardiac output, (2) insufficient myocardial contraction to produce cardiac output [pulseless electrical activity (PEA)] and (3) complete failure of the electrical conduction system of the heart (asystole).

Manifestation of OHCA is dramatic: blood supply to the brain and vital organs ceases within seconds, the patient loses consciousness and the process of cell death commences. The window of opportunity to achieve return of spontaneous circulation (ROSC) is very narrow: a matter of minutes. Delays in attempts to restart the heart have catastrophic consequences, increasing the likelihood of death or severe neurological injury. Prolonged duration of resuscitation attempts is associated with poor outcomes.

The Department of Health and Social Care's *Cardiovascular Disease Outcomes Strategy: Improving Outcomes for People With or at Risk of Cardiovascular Disease*,[4] published in 2013, estimated that an increase in the survival rate from OHCA in England of between 10% and 11% could save > 1000 lives each year. *Resuscitation to Recovery: A National Framework to Improve Care of People with Out-of-Hospital Cardiac Arrest (OHCA) in England*,[5] was published in 2017, providing a consensus on the optimal pathway for OHCA in England. Research to improve understanding of resuscitation from OHCA was identified as a national priority. Similar initiatives have been published in the devolved nations.[6–8]

Chain of survival

The chain of survival[9] concept (*Figure 1*) is recognised internationally and summarises the key components of the response to OHCA to optimise the chances of survival. The links in the chain are discussed in more detail in the following sections.

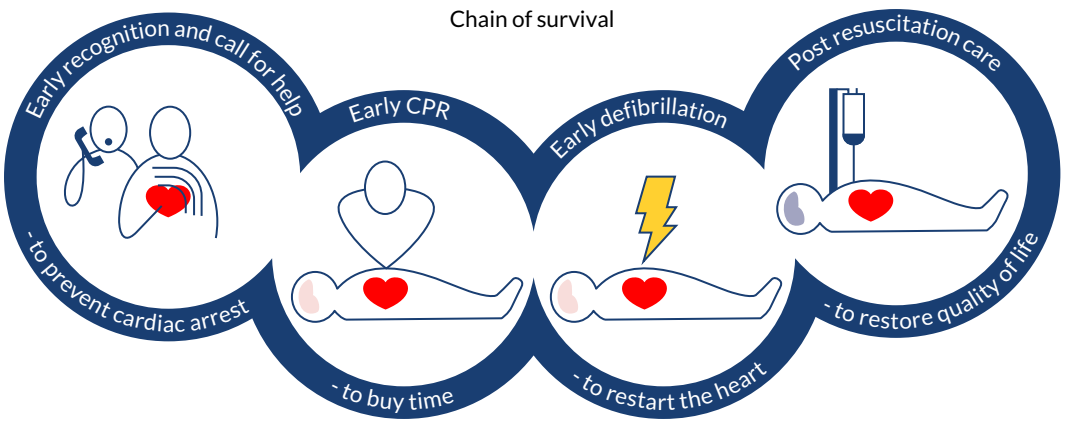

FIGURE 1 The chain of survival.[9] CPR, cardiopulmonary resuscitation. Reprinted from *Resuscitation*, Vol. 71, Nolan J, Soar J, Eikeland H, The chain of survival, pp. 270–1, Copyright 2006, with permission from Elsevier.

Early access

The first link in the chain highlights that it is important to identify a patient at risk of cardiac arrest (e.g. someone with an acute coronary syndrome) or a patient who has suffered a cardiac arrest (signs of which are loss of consciousness and absence of normal breathing). Rapid identification and calling for help early allow the ambulance service to send a trained advanced life support team to them as quickly as possible.

Raising public awareness of OHCA and the steps members of the public can take to increase chances of survival [calling 999 immediately and commencing cardiopulmonary resuscitation (CPR)] are the subject of major campaigns led by the British Heart Foundation and Resuscitation Council (UK), voluntary aid societies such as St John Ambulance and British Red Cross, and NHS ambulance services. World 'Restart a Heart' Day is an annual initiative that aims to train as many people as possible in CPR in 1 day.[10] NHS England has led work on improving ambulance call-taker's recognition of life-threatening emergencies such as cardiac arrest, based on information provided by the person calling 999/111, as a component of the Ambulance Response Programme.[11] Ambulance telephone triage using NHS Pathways to identify OHCA accurately identifies 75% of adult OHCA {sensitivity 0.759 [95% confidence interval (CI) 0.473 to 0.773], specificity 0.986 (95% CI 0.9858 to 0.98647), positive predictive value 26.80% (95% CI 25.88 to 27.73)}.[12] This facilitates despatch of an ambulance response with the highest priority, and the provision of advice and support to the caller on how to perform CPR pending arrival of trained personnel. In other countries, such as Singapore, a comprehensive programme of ambulance dispatcher telephone support was associated with a doubling in bystander CPR rates.[13] When the ambulance service is aware of a nearby defibrillator, there is an opportunity to direct the caller and/or another responder to retrieve this, provided this does not delay or interrupt bystander CPR (see *High-quality cardiopulmonary resuscitation*).

High-quality cardiopulmonary resuscitation

Cardiopulmonary resuscitation is the combination of chest compressions and ventilations, and is optimally started by those initially at the scene of the collapse (bystander CPR). Bystander CPR increases the odds of survival by 1.23 (95% CI 0.71 to 2.11) in the studies with the highest baseline survival rates, to 5.01 (95% CI 2.57 to 9.78) in the studies with the lowest baseline rates.[14] When the emergency medical services (EMS) arrive on scene, they will take over CPR. Current resuscitation guidelines highlight the importance of high-quality CPR for ensuring optimal outcomes from cardiac arrest.[15] High-quality CPR is CPR that ensures an adequate chest compression depth is achieved (5–6 cm), that the compression rate is 100–120 per minute, that interruptions are minimised (for rhythm check/defibrillation and during extrication) and that the chest is allowed to recoil between chest compressions.

There are no randomised trials evaluating different compression parameters. Nevertheless, high-quality CPR appears to be important for outcomes.[16] Experimental studies show a linear increase in cardiac output and coronary perfusion pressure with increasing compression depths.[17,18] Observational studies in humans found improved defibrillator shock success[19] and trends towards better ROSC rates and long-term survival with deeper chest compressions.[20] Faster chest compression rates (> 100 per minute) are associated with improved survival[21,22] and ensuring that the chest is allowed to recoil between sequential chest compressions also appears to be important.[23]

Interruptions in CPR are harmful.[24] A particularly critical time to minimise interruptions to CPR is around the time of attempted defibrillation. Prolonged pre-shock and peri-shock interruptions in CPR reduce the chances of shock success[19] and survival.[25]

Mechanical chest compression has not been shown in randomised trials to improve the outcome of OHCA.[26]

Early defibrillation

Approximately one-quarter of OHCAs in the UK are due to an arrhythmia either VF or pulseless VT. These rhythms are referred to as shockable rhythms, as the arrhythmias may be terminated and cardiac function restored by the successful delivery of defibrillator shocks. The time from the onset of VF/VT to the delivery of a shock is critical to shock success and the chances of survival. For every 60–90 seconds that a shock is delayed, the chances of survival fall by approximately 10%.[27]

If a defibrillator is immediately available at the scene of a cardiac arrest, defibrillation should be attempted without delay. When there is a delay in applying a defibrillator, there is a theoretical rationale that providing CPR before a shock improves coronary perfusion and, therefore, the chances of achieving sustained ROSC.[28]

This concept was evaluated by the Resuscitation Outcomes Consortium (ROC) in a cluster randomised trial comparing early analysis (30–60 seconds of EMS-administered CPR before initial rhythm analysis) with later analysis (180 seconds of CPR before the initial electrocardiographic analysis).[29] The primary outcome was survival to hospital discharge with satisfactory functional status [a modified Rankin Scale (mRS) score of ≤ 3, on a scale of 0–6, with higher scores indicating greater disability]. The trial enrolled 9933 patients (5290 to early analysis and 4643 to late analysis) but found no difference in outcomes (cluster-adjusted difference of –0.2%, 95% CI –1.1% to 0.7%).

Public access defibrillation (PAD) has the potential to improve outcomes of OHCA. A national scheme led by the Department of Health and Social Care was launched in England in 1999 and was focused on busy public places such as railway stations.[30] ROSC was reported for 170 out of 437 (39%) patients, and hospital discharge was reported for 113 out of 437 (26%) patients.[31] A systematic review of observational studies reported an overall median survival of 40% (range 9–83.3%) in OHCA patients treated by PAD, with defibrillation by bystanders associated with median survival rates of 53% (range 26–72%).[32] In a further systematic review, bystander automated external defibrillator (AED) use was associated with survival to hospital discharge [odds ratio (OR) 1.66, 95% CI 1.54 to 1.79] and favourable neurological outcome (OR 2.37, 95% CI 1.58 to 3.57) in patients with shockable rhythms. However, the quality of the evidence quality was deemed to be low to very low.[33]

Public access defibrillators are underutilised in OHCA. A retrospective review of OHCA in Hampshire reported that callers had access to an AED in 44 (4.2%) OHCA cases, and that AEDs were used before ambulance arrival in only 18 (1.7%) cases.[34] A systematic review of barriers to and facilitators of the use of PADs identified a range of themes, including knowledge and awareness, willingness to use, acquisition and maintenance, availability and accessibility, training issues, registration and regulation, medicolegal issues, EMS dispatch-assisted use of AEDs, AED locator systems, demographic factors, and other behavioural factors. The quality of the evidence was deemed to be very low.[35] Deakin *et al.*[36] recently mapped 4012 OHCAs to 2076 AEDs known to the South Central Ambulance Service, and reported that only 5.9% of the AEDs were within a 100 m radius of OHCA locations during daytime, falling to 1.59% during out of hours.

Adrenaline

Treatment with adrenaline has been an integral component of advanced life support from the birth of modern CPR in the early 1960s. In guidelines written originally in 1961, Safar[37] recommended the use of adrenaline: 1 mg intravenously or 0.5 mg intracardiac. Adrenaline has been recommended in successive guidelines from around the world. An analysis of drug use across 264 EMS agencies in the USA and Canada reported that 81% (range 57–98%) of patients experiencing an OHCA received adrenaline.[38] The Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) registry reported that 77.5% of patients in England and Wales received adrenaline as part of their treatment for OHCA.[39]

Animal studies show that injection of adrenaline during cardiac arrest increases aortic tone, thereby augmenting coronary blood flow.[40,41] However, there are limited reliable data to assess the effects of

adrenaline on long-term outcomes after cardiac arrest. The International Liaison Committee on Resuscitation (ILCOR) synthesised the available evidence for adrenaline in 2010 (also reassessed in October 2012) and noted that, although adrenaline may improve the rate of ROSC and short-term survival, there is insufficient evidence to suggest that adrenaline improves survival to discharge from hospital and neurological outcome. ILCOR stated that placebo-controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest are needed.[42]

Post-resuscitation care

The ROSC marks the start of the post-resuscitation care phase of treatment.[43] Unless the arrest has been relatively brief, most patients who achieve ROSC will have an obtunded consciousness level, necessitating admission to intensive care. The focus of the post-resuscitation care phase of treatment is stabilising cardiac function to prevent further cardiac arrest and minimising the consequences of the cardiac arrest on neurological outcome. This involves the use of targeted temperature management, the avoidance of hyperglycaemia and coronary angiography to guide coronary reperfusion, if required. Post-resuscitation care treatments are initiated by ambulance clinicians and continue after the patient's arrival in the emergency department (ED) and in the intensive care unit (ICU). Patients with ROSC who have evidence of ST-segment elevation on a 12-lead electrocardiogram (ECG) are transferred directly to the cardiac catheter laboratory for urgent angiography revascularisation, if appropriate, in accordance with National Institute for Health and Care Excellence (NICE) guidance.[44] A recent randomised clinical trial suggested no benefit for urgent angiography in post-cardiac arrest patients without ST-segment elevation on a 12-lead ECG,[45] but other trials evaluating the role of urgent coronary angiography in these patients are ongoing.[46–51]

Incidence and burden of disease

The societal burden of OHCA has been described as equal to or greater than that of other leading causes of death.[52] Each year, an estimated 275,000 people in Europe experience an OHCA, with < 30,000 surviving to hospital discharge.[53] The UK OHCA outcome project, a prospective observational study involving all UK NHS ambulance services, reported that 28,729 patients were treated for OHCA by the 10 ambulance services in England in 2014 (53/100,000 population), with 7.9% surviving to hospital discharge.[2] Globally, estimates of OHCA outcomes vary across countries, with survival to hospital discharge rates of 7.6% in Europe, 6.8% in North America, 3% in Asia and 9.7% in Australia.[54]

Out-of-hospital cardiac arrest exerts a major burden on NHS resources (ambulance response, emergency treatment, post-resuscitation care, rehabilitation) and years of life lost, but treatment currently has a low chance of success.

Existing evidence

A Cochrane review[55] identified a single randomised, placebo-controlled trial of intravenous (i.v.) adrenaline in OHCA (the search was conducted in December 2012). The Pre-hospital Adrenaline for Cardiac Arrest (PACA) trial,[56] conducted by our co-investigators Judith Finn and Ian G Jacobs, was undertaken in Western Australia. The study aimed to enrol 5000 patients, but, at the time the study closed, only 601 patients had been randomised. The relatively small numbers led to the results having large uncertainty. The rate of ROSC (short-term survival) was higher in those receiving adrenaline [64/272 (23.5%) vs. 22/262 (8.4%) patients; OR 3.4, 95% CI 2.0 to 5.6], but there was no clear evidence of a benefit in survival to hospital discharge (long-term survival) [adrenaline arm, 11 (4.0%) patients, vs. placebo arm, 5 (1.9%) patients; OR 2.2, 95% CI 0.7 to 6.3]. Two of the survivors in the adrenaline arm, but none in the placebo arm, had a poor neurological outcome. In addition to the trial's imprecision, interpretation of the findings is limited by a large number of post-randomisation exclusions ($n = 67$, 11%).

A second randomised study, conducted in Oslo, Norway, compared i.v. cannulation and injection of drugs (including adrenaline) with no i.v. cannula or drugs among 851 patients experiencing an OHCA.[57] The patients in the i.v. arm had better short-term survival rates [ROSC: i.v. arm, 165/418 (40%), vs. no i.v. arm, 107/433 (25%); OR 1.99, 95% CI 1.48 to 2.67]; however, there was no clear difference between arms in long-term survival outcomes {survival to hospital discharge: i.v. arm, 44/418 (10.5%), vs. no i.v. arm, 40/433 (9.2%); OR 1.16, 95% CI 0.74 to 1.82; favourable neurological outcome [measured using the Cerebral Performance Category (CPC) 1 or 2]: i.v. arm, 9.8%, vs. no i.v. arm, 8.1%; OR 1.24, 95% CI 0.77 to 1.98}. The increase in the rate of ROSC was seen mainly in the patients with initial non-shockable rhythms (asystole and PEA): 29% in the i.v. arm versus 11% in the no i.v. arm. The rate of ROSC was 59% in the i.v. arm, compared with 53% in the no i.v. arm, in those patients with an initial rhythm of VF/VT.

In the post hoc analysis of the i.v. versus no-i.v. trial, outcomes were examined according to whether or not a patient had actually received adrenaline.[58] Treatment with adrenaline ($n = 367$) was associated with a greater chance of being admitted to hospital (OR 2.5, 95% CI 1.9 to 3.4). However, long-term survival outcomes were worse, with reduced survival to hospital discharge [adrenaline arm, 24/367 (7%), vs. no adrenaline arm, 60/481 (13%); OR 0.5, 95% CI 0.3 to 0.8] and reduced neurologically intact (CPC 1 or 2) survival [adrenaline arm, 19/367 (5%), vs. no adrenaline arm, 57/481 (11%); OR 0.4, 95% CI 0.2 to 0.7]. These effects persisted after adjustment for confounding factors (VF, response interval, witnessed arrest, sex, age and tracheal intubation).

At the time of developing the Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest 2 (PARAMEDIC2) trial, three large observational studies[59–61] suggested that adrenaline may cause worse long-term outcomes. The largest observational study of adrenaline use in cardiac arrest involves 417,188 OHCAs in Japan.[59] In propensity-matched patients, use of adrenaline was associated with an increased rate of ROSC [adjusted odds ratio (aOR) 2.51, 95% CI 2.24 to 2.80], but was also associated with a 1-month survival rate of approximately half that achieved among those not given adrenaline (aOR 0.54, 95% CI 0.43 to 0.68). In another observational study from the Osaka group in Japan,[60] 1013 (32.0%) of 3161 patients who were analysed received adrenaline. Those patients receiving adrenaline had a significantly lower rate of neurologically intact (CPC 1 or 2) 1-month survival than those not receiving adrenaline (4.1% vs. 6.1%, respectively; OR 0.69, 95% CI 0.48 to 0.98).

An analysis of registry data had shown reduced survival in those who received adrenaline; The North American ROC Epistry ($n = 16,000$) found an inverse association between adrenaline dose and survival to discharge (survival was > 20% for those not requiring adrenaline, and fell to < 5% for those requiring more than two doses). This finding persisted after adjustment for age, sex, EMS-witnessed arrest, bystander-witnessed arrest, bystander CPR, shockable initial rhythm, time from 911 call to EMS arrival, the duration of OHCA and study site.[38] This was similar to a previous analysis of the Swedish Registry ($n = 10,000$ patients; OR of long-term survival 0.43, 95% CI 0.27 to 0.66).[61]

This creates the paradox of better short-term survival at the cost of worse long-term outcomes, in other words a 'double-edged sword'.[62] However, observational studies are limited by the influence of confounding variables that may introduce bias, in particular the phenomenon known as resuscitation time bias, whereby an exposure is more likely to occur the longer the cardiac arrest continues. Because duration of resuscitation is strongly associated with worse outcome, this will bias the results towards a harmful effect of the exposure.[63] The importance of differences in analytical approaches and the way they control for resuscitation time bias is illustrated by the discordant findings from the analysis of the same data set, whereby one study shows benefit[64] and the other demonstrates harm.[59]

Mechanisms by which adrenaline may cause harm

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

Reduced microvascular blood flow and exacerbation of cerebral injury

In animal models of cardiac arrest, adrenaline increases coronary perfusion pressure (which predicts restarting the heart), but impairs macrovascular and microvascular cerebral blood flow. Specifically, adrenaline was noted to reduce carotid blood flow[65] and microvascular blood flow,[29] causing worsening cerebral ischaemia.[66]

Cardiovascular toxicity

In a further analysis of the Norwegian i.v. versus no i.v. trial,[57] adrenaline increased the frequency of transitions from PEA to ROSC and extended the time window for ROSC, but at a cost of greater cardiovascular instability after ROSC, with a higher rate of re-arresting. These observations were consistent with other studies that linked adrenaline with ventricular arrhythmias and increased post-ROSC myocardial dysfunction.[67] In human studies with patients with sepsis[68] or acute lung injury,[69] beta-agonist stimulation was similarly linked to cardiovascular instability and reduced survival.[70] A systematic review of beta-blocker treatment in animal models of cardiac arrest found that fewer shocks were required for defibrillation; that myocardial oxygen demand was reduced; and that post-resuscitation myocardial stability improved, with less arrhythmia and improved survival.[71]

Metabolic effects

Adrenaline causes lactic acidosis,[72] which is associated with poor outcomes after cardiac arrest.[73,74] It also induces stress hyperglycaemia, which is also associated with poorer outcomes.[75]

Immunomodulation and predisposition to infection

Infective complications, including bacteraemia and early-onset pneumonia, are common after OHCA, and are associated with worse outcomes.[76] The immune-modulatory effects of beta agonists have been well characterised and may reduce host defence against infection,[77] which may contribute to an increased susceptibility to post-resuscitation sepsis.

Summary of effects

Use of adrenaline in cardiac arrest increases short-term survival (i.e. ROSC), but doubt remained about whether or not this translated into better long-term outcomes.

Rationale for intervention

Whether or not the practice of giving adrenaline is effective remained an important question that needed to be answered. Uncertainty about adrenaline has been raised by recent evidence[59–61] suggesting that it may be harmful. Resolving this uncertainty was urgent, as adrenaline is used widely to treat cardiac arrests, and, if harmful, may be responsible for many avoidable deaths. There have been several precedents whereby treatments have been evaluated after years or decades of use and had been found to be ineffective or harmful, including pulmonary artery catheters in intensive care,[78] beta agonists for acute respiratory distress syndrome[69] and corticosteroids for head injury.[79] It was therefore possible that adrenaline for cardiac arrest might be a similar case.

The ILCOR appraised the evidence surrounding adrenaline use for OHCA in 2010[42] and again in October 2012. It concluded that there was an urgent need for randomised, placebo-controlled trials of adrenaline.

We conducted a written survey of 213 attendees (doctors, nurses, paramedics) of the Resuscitation Council (UK) Annual Scientific Symposium in September 2012 to assess the scientific and clinical communities' current perspectives on the role of adrenaline in the treatment of cardiac arrest. Respondents expressed their agreement to a series of statements on a seven-point Likert scale (1 = strongly disagree, 7 = strongly agree). Respondents reported that adrenaline increased short-term survival [median score 6, interquartile range (IQR) 6–7], but disagreed that it improved long-term

outcomes [median score 2 (IQR 2–3)]. The greatest uncertainty was around the balance of risks and the benefits of i.v. adrenaline (*Figure 2*). Respondents felt that the most pressing future research need for the NHS was a trial comparing adrenaline with placebo (*Figure 3*).

A trial addressing this question was timely, because of the recent publication of studies questioning the effectiveness of adrenaline, and calls for a large-scale randomised controlled trials to resolve this issue. There were no other completed, ongoing or planned trials in the ClinicalTrials.gov [https://clinicaltrials.gov/ (1 January 2012)] or controlled-trials.com (accessed 2012) databases. Moreover, research projects [e.g. the Prehospital Randomised Assessment of a Mechanical compression Device In Cardiac arrest (PaRAMeDIC) trial[81] in 2010] had shown the feasibility of conducting large-scale OHCA trials in the UK. The learning from the PaRAMeDIC trial,[81] undertaken by this group, helped to ensure efficient and successful recruitment.

The emerging data suggested that a number of experimental strategies could be considered, including comparing adrenaline with alpha 2 agonists, comparing adrenaline with beta blockade, lower-dose adrenaline or adrenaline as a continuous infusion. Preferences of the clinical community are summarised in *Figure 3*. The timing of adrenaline administration may also be important; however,

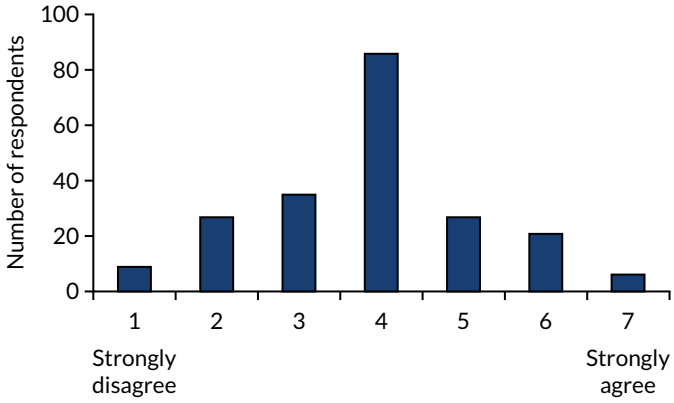

FIGURE 2 Perspectives of the UK clinical community on the role of adrenaline for the treatment of cardiac arrest.[80] Reprinted from *Resuscitation*, Vol. 108, Perkins GD, Quinn T, Deakin CD, Nolan JP, Lall R, Slowther A, *et al.*, Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): trial protocol, pp. 75–81, Copyright 2016, with permission from Elsevier.

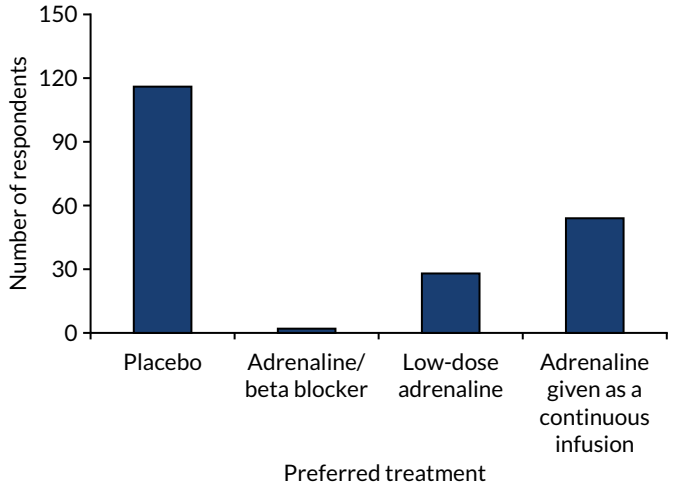

FIGURE 3 Preferences of the UK clinical community.[80] Reprinted from *Resuscitation*, Vol. 108, Perkins GD, Quinn T, Deakin CD, Nolan JP, Lall R, Slowther A, *et al.*, Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): trial protocol, pp. 75–81, Copyright 2016, with permission from Elsevier.

this was primarily dependent on ambulance response times, which were difficult to control for in a randomised trial. We suggested that the most pressing need was for a definitive trial comparing standard-dose adrenaline (1 mg every 3–5 minutes) with placebo. Until there was clarity about the effect of adrenaline on long-term outcomes, the best comparator agent (placebo or standard-dose adrenaline) for trials of other agents remained unknown.

This randomised controlled trial of adrenaline had the support of key stakeholders, such as patient representatives, the College of Paramedics, the National Ambulance Services Medical Directors' Group, the Joint Royal Colleges Ambulance Liaison Committee (JRCALC), the Resuscitation Council (UK) and the British Heart Foundation.

Objectives

Primary objective

The primary objective of this trial was to determine the clinical effectiveness of adrenaline in the treatment of OHCA, measured as a primary outcome of 30-day survival.

Secondary objective

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

Chapter 2 Methods

Trial design

This was a pragmatic, randomised, allocation-concealed, placebo-controlled, parallel-group superiority trial and economic evaluation. Participants were randomised to either adrenaline (intervention) or placebo (control) in a 1 : 1 allocation ratio. Randomisation took place when a trial-trained paramedic opened an Investigational Medicinal Product (IMP) pack, which contained either 10 syringes of adrenaline (1 mg) or a matching placebo (0.9% saline). The primary outcome was survival to 30 days. Secondary outcomes focused on patient, clinical, resource and economic outcomes. Patients, clinical teams and those assessing patient outcomes were masked to the treatment allocation.

Figure 4 shows the planned flow of participants through the trial.

Pilot trial

An internal pilot was run to test that the components of this trial worked together. This pilot ran for 6 months. The data from this were included in the main trial. During the pilot, we measured recruitment rate and compliance with the allocated intervention, and checked that the approach to data collection and follow-up worked effectively. The pilot phase ran seamlessly into the main trial. The results of the pilot trial were reviewed with the Trial Steering Committee (TSC), the Data Monitoring Committee (DMC) and representatives from the Health Technology Assessment (HTA) programme, specifically considering the achievement of the following targets:

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

All pilot objectives were achieved, and the TSC approved continuation to the main phase of the trial on 7 May 2015.

Changes to trial design

There were no substantial changes to the trial design. *Table 1* lists all amendments to the trial and details of the changes made. *Reasons for changes to the trial design* describes the reason for the change in exclusion criteria (amendment 6).

Reasons for changes to the trial design

Amendment 4

This amendment updated the Research Ethics Committee (REC) application to confirm that participants who were prisoners or young offenders in the custody of Her Majesty's Prison Service or who were offenders supervised by the probation service in England or Wales would be included in the trial.

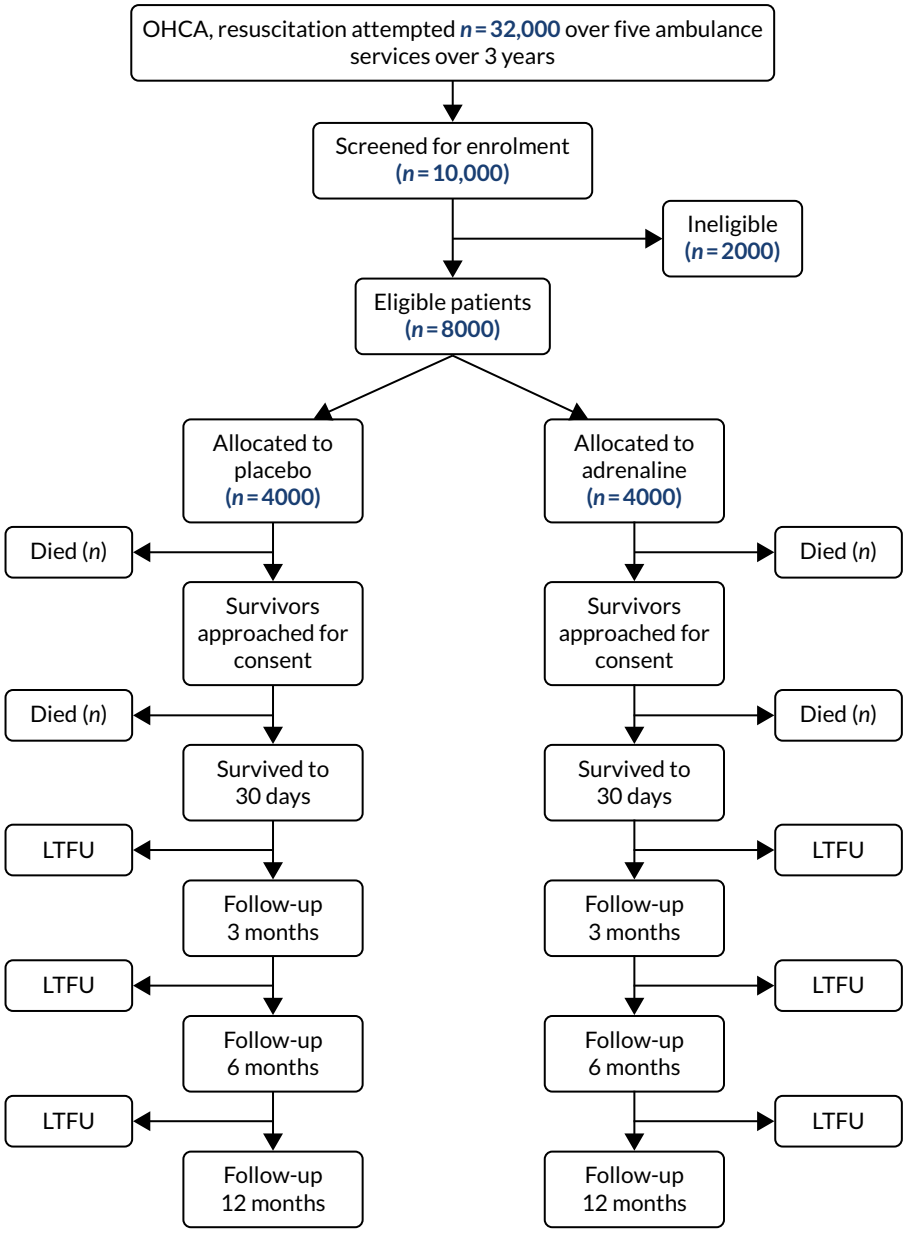

FIGURE 4 Flow chart for PARAMEDIC-2 trial.[80] LTFU, lost to follow-up. Reprinted from *Resuscitation*, Vol. 108, Perkins GD, Quinn T, Deakin CD, Nolan JP, Lall R, Slowther A, *et al.*, Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): trial protocol, pp. 75–81, Copyright 2016, with permission from Elsevier.

The rationale for not excluding prisoners was as follows:

- There may be practical difficulties in identifying a prisoner in an emergency situation.
- Attempting to establish if someone is a prisoner may lead to confusion and delay of treatment, which may cause harm.
- Prisoners are not being recruited to the trial because of their position as prisoners, they are being recruited because of their interaction with the NHS in a cardiac arrest situation.
- It would be unethical to deny prisoners the rights to the potential benefits of the trial.

TABLE 1 Amendments to trial

Date of amendment	Number	Document(s) affected	Changes	New version number; date	Date approved by MHRA	Date approved by REC
2 August 2018	21	Unblinding response form	Unblinding response form updated	v2.0; 7 August 2018	N/A	14 August 2018
		Unblinding information sheet	Unblinding information sheet updated and separated into three versions (non-survivor, survivor with poor neurological outcome, and survivor with good neurological outcome)	v2.0; 2 August 2018		
25 July 2018	20	Protocol	• Project end date extended to 31 July 2018 • Change to protocol wording in sections 3.2.3 and 5.1 to include the collection of patient-level data from the UK Transplant Registry	v6.0; 25 July 2018	N/A	13 November 2018
26 March 2018	19	Protocol	• Change to protocol wording in sections 3.2.3 and 5.1 to include the collection of patient-level data from the PEDW • Section 2.9.3 added to include methods for unblinding treatment allocation after completion of the trial	v5.0; 28 March 2018	N/A	3 April 2018
		Unblinding information sheet	New document to be able to respond to requests for unblinding	v1.0; 28 March 2018		
		Unblinding response form	New document to be able to respond to requests for unblinding	v1.0; 28 March 2018		
		Unblinding cover letter for response form	New document to be able to respond to requests for unblinding	v1.0; 28 March 2018		
		Confirmation of treatment letter	New document to be able to respond to requests for unblinding	v1.0; 28 March 2018		

continued

TABLE 1 Amendments to trial (*continued*)

Date of amendment	Number	Document(s) affected	Changes	New version number; date	Date approved by MHRA	Date approved by REC
28 February 2018	18	Protocol	Section 2.6.15.1 added to describe the process for responding to trial participation enquiries	v4.0; 28 February 2018	N/A	28 February 2018
		Cover letter (patient enrolled)	New document produced to be able to respond to trial participation enquiries	v1.0; 28 February 2018		
		Cover letter (patient not enrolled)	New document produced to be able to respond to trial participation enquiries	v1.0; 28 February 2018		
		Trial participation information sheet	New document produced to be able to respond to trial participation enquiries	v1.0; 28 February 2018		
13 March 2017	17	N/A	Addition of hospital (Medway)	N/A	N/A	17 March 2017
23 January 2017	16	N/A	Addition of general practice surgeries as sites to allow mRS data collection under HRA approval	N/A	N/A	23 January 2017
13 December 2016	15	N/A	Addition of two hospital sites (Luton and Dunstable, and Bedford)	N/A	N/A	20 December 2016
24 November 2016	14	N/A	Translations and back translations of patient information sheet, consent forms and cover letters into Arabic, Gujarati, Hindi, Polish, Punjabi, Urdu and Welsh	N/A	N/A	14 December 2016
2 November 2016	13	GP letter (mRS)	New letters for GPs to collect mRS data (two versions – one for consent and one for passive follow-up)	v1.0; 1 November 2016	N/A	18 November 2016
21 October 2016	12	Protocol	Addition of quality of CPR data collection	v3.0; 12 October 2016	27 October 2016	31 October 2016

Date of amendment	Number	Document(s) affected	Changes	New version number; date	Date approved by MHRA	Date approved by REC
1 June 2016	11	Protocol	• Section 2.5.2 (exclusion criteria) clarification added • Section 2.9.2 (unblinding) updated • Section 3.2.4 (quality of CPR) added • Section 4.2 (SAEs) clarification added • Section 5.1 (data collection) updated to include Hospital Episode Statistics and Office for National Statistics data • Other minor amendments	v2.0; 4 May 2016	N/A	20 June 2016
		Patient information sheets	• Separate versions created for approach in hospital or after hospital discharge • Wording updated as required by NHS Digital to obtain mortality data	v2.0; 8 April 2016		
		Patient information sheets cover letters	Separate versions created for patient and legal representative and approach in hospital or after hospital discharge	v2.0; 8 April 2016		
		Consent forms	Wording updated to include reference to Health and Social Care Information Centre (former name of NHS Digital) and Office for National Statistics	v2.0; 8 April 2016 (note that the legal representative consent form was amended to v2.1 because of a typographical error)		
28 October 2015	10	N/A	Addition of four hospitals (Burton Hospitals NHS Foundation Trust, Western Sussex Hospitals NHS Foundation Trust, University Hospitals Bristol and Weston NHS Foundation Trust, and Countess of Chester Hospital NHS Foundation Trust)	N/A	N/A	6 November 2015

continued

TABLE 1 Amendments to trial (*continued*)

Date of amendment	Number	Document(s) affected	Changes	New version number; date	Date approved by MHRA	Date approved by REC
28 October 2015	9	GP letter	GP letter about survival and mRS scores for non-responders	v1.0; October 2015	N/A	9 November 2015
8 September 2015	8	IMP dossier	Revision of IMP dossier to extend IMP shelf life to 12 months	4.0	15 October 2015	9 November 2015
10 July 2015	7	N/A	Addition of Royal Surrey County Hospital	N/A	N/A	23 July 2014
24 June 2015	6	Protocol	Addition of 'cardiac arrest secondary to life-threatening asthma' as exclusion criterion	1.1; 24 June 2015	13 July 2015	8 July 2015
11 May 2015	5	Poster for public '10 Facts about the PARAMEDIC2 trial'	New document to raise public awareness of trial	1.0; 12 May 2015	N/A	22 May 2015
		Leaflet for general practice surgeries	New document to raise public awareness of trial	1.0; 12 May 2015		
		Communication strategy	Revised document	11 May 2015		
3 December 2014	4	N/A	Clarification that prisoners would not be excluded from the trial	N/A	N/A	4 December 2014
8 October 2014	3	N/A	Addition of English hospitals	N/A	N/A	8 October 2014
4 September 2014	2	N/A	Addition of Welsh hospitals: Bronglais General Hospital, Glan Clwyd Hospital, Glangwili General Hospital, Morriston Hospital, Nevill Hall Hospital, Prince Charles Hospital, Princess of Wales Hospital, Prince Philip Hospital, Royal Glamorgan Hospital, Royal Gwent Hospital, University Hospital of Wales, Withybush General Hospital, Wrexham Maelor Hospital, Ysbyty Gwynedd, Singleton Hospital, West Wales General Hospital and Llandough Hospital	N/A	N/A	9 September 2014

Date of amendment	Number	Document(s) affected	Changes	New version number; date	Date approved by MHRA	Date approved by REC
27 August 2014	1	Patient information sheet	Updated following feedback from CAG	• 1.1; 4 July 2014 • 1.2; 5 September 2014	N/A	10 October 2014
		Consent forms (patient and legal representative)	Updated following feedback from CAG	• 1.1; 4 July 2014 • 1.2; 5 September 2014		
		Cover letter (patient and legal representative)	Updated following feedback from CAG	• 1.1; 4 July 2014 • 1.2; 5 September 2014		
		Poster for public 'OK to Ask'	New document to raise public awareness of trial	• 1.1; 27 August 2014 • 1.2; 4 September 2014		
		REC form Part C	WAST principal investigator corrected to Nigel Rees	N/A		

CAG, Confidentiality Advisory Group; GP, general practitioner; HRA, Health Research Authority; MHRA, Medicines and Healthcare products Regulatory Agency; N/A, not applicable; PEDW, Patient Episode Database for Wales; REC, Research Ethics Committee; SAE, serious adverse event; WAST, Welsh Ambulance Service.

Amendment 6

Cardiac arrest secondary to life-threatening asthma was added as a trial exclusion criterion following amendment 6 on 24 June 2015. Although the published literature points to there being equipoise about the use of i.v. adrenaline in asthma,[82–85] there is evidence that adrenaline may be beneficial for patients with anaphylaxis. The rationale for the change was that, during the pilot trial, ambulance staff were concerned about potential overlap between the presentation of asthma and anaphylaxis (both may present with bronchospasm). Therefore, the Trial Management Group (TMG) felt that the safest option was to extend the exclusion for anaphylaxis to include cardiac arrests suspected to have been caused by asthma.

Eligibility criteria

Inclusion criteria

Patients were eligible if both the following criteria were met:

- cardiac arrest in an out-of-hospital environment
- advanced life support initiated and/or continued by an ambulance service clinician.

Exclusion criteria

The exclusion criteria at the time of arrest were as follows:

- known or apparent pregnancy
- known to be or apparently aged < 16 years
- cardiac arrest caused by anaphylaxis or life-threatening asthma
- adrenaline given prior to arrival of ambulance service clinician.

In London Ambulance Service, traumatic cardiac arrests were also excluded, in accordance with local protocols.

Trial setting

Recruitment took place in five NHS ambulance services in the UK (London Ambulance Service NHS Trust, North East Ambulance Service NHS Foundation Trust, South Central Ambulance Service NHS Foundation Trust, West Midlands Ambulance Service University NHS Foundation Trust and Welsh Ambulance Service NHS Trust). These ambulance services serve a mix of urban and rural locations in England and Wales, covering a population of 24 million people. They collectively attend ≈32,000 cases of cardiac arrest each year; resuscitation is attempted or continued by ambulance staff in approximately 45% of these cases.

The ambulance services are activated through a central emergency call number (999, 112 or 111), which directs the caller to the geographically relevant emergency operations and dispatch centre. Calls are received and processed by trained NHS ambulance dispatch staff. Dispatch staff use one of two dispatch support systems: NHS Pathways or Advanced Medical Priority Dispatch System. Cases identified as a cardiac arrest are assigned the highest priority response. At the time of the trial, ambulance services were expected to provide a defibrillation-capable response within 8 minutes for 75% of these cases. There was an expectation of having an ambulance on scene within 19 minutes in 95% of cases. A typical first response could be a community first responder, a rapid response vehicle (e.g. car, motorbike or bicycle) or an air/land ambulance. Clinically trained staff, such as paramedics or emergency medical technicians, typically attend cardiac arrests. They are often supported by emergency care assistants. Paramedics can deliver advanced life support (ALS) interventions (including advanced airway management and i.v. drugs) and, after trial-specific training, were able to recruit patients to the trial. Technicians, emergency care assistants and many

community responders dispatched by the NHS ambulance service can deliver CPR and defibrillation, and some use supraglottic airways. When ambulance staff arrive at a cardiac arrest, one of the first steps is for them to assess the appropriateness of a full resuscitation attempt. If there is unequivocal evidence of death (major traumatic injuries, putrefaction, rigour mortis, post-mortem staining, etc.) NHS guidelines[86] allow resuscitation to be withheld. Other situations in which resuscitation may be withheld are when a patient has a 'do not attempt cardiopulmonary resuscitation' instruction, if the patient is in asystole, if no bystander CPR has been performed or if > 15 minutes have elapsed since the time of collapse.[87] Ambulance services follow common national guidelines for resuscitation from the Resuscitation Council UK guidelines,[86] which follow those provided by the European Resuscitation Council.[88] The overall UK rate of survival to discharge for all cases of OHCA for which resuscitation is attempted is 7.9%.[89]

Trial intervention

Patients were enrolled in the trial by the attending ambulance service clinicians, who determined whether or not a resuscitation attempt was appropriate (according to the JRCALC guidelines[87]), and, if it was, whether or not the patient was eligible. Patients who met the eligibility criteria were randomised to the trial.

Patients received resuscitation according to the Resuscitation Council (UK) and JRCALC ALS guidelines.[86] All standard ALS interventions were provided, including chest compression, defibrillation and advanced airway management, as required, with the exception that standard adrenaline was substituted with trial IMP drawn from a single trial treatment pack. Vehicles also carried their standard supply of adrenaline, for use only with ineligible patients.

If the patient reached the point in the resuscitation protocol where pharmacological treatments were indicated, they were randomly assigned to receive either parenteral adrenaline or saline placebo by the opening of a trial drug pack. Each treatment pack contained 10 × 3-ml prefilled syringes, with each syringe containing either 1 mg of adrenaline (intervention) or 0.9% saline (control). All trial drug packs were labelled with a unique trial pack number and in accordance with EudraLex Volume 4 Annex 13 requirements.[90] The adrenaline and placebo packs and syringes were identical in appearance; therefore, clinicians, patients and trial personnel were unaware of whether any specific pack contained adrenaline or placebo.

Single doses of adrenaline or saline were administered every 3–5 minutes by an i.v. or intraosseous route. Clinicians were instructed to use only one treatment pack per patient (10 × 3-ml syringes). Treatments were continued until a sustained pulse was achieved, resuscitation was discontinued or care was handed over to the clinician at the receiving hospital.

Treatment after admission to hospital was not specified in the trial protocol, but was informed by national guidelines,[91] which covered targeted temperature management, haemodynamic and ventilator criteria and prognostication.

Randomisation

As recruitment took place in an emergency situation, telephone or internet randomisation was impractical; therefore, the trial used a system of pre-randomised treatment packs. The trial IMP was packaged in numbered treatment packs. The pre-randomised sequence was prepared by the programmers at the Warwick Clinical Trials Unit (WCTU). The randomisation sequence was computer generated by the stratified randomisation method with concealed assignment, using ambulance service as a strata, with an allocation ratio of 1 : 1.

Treatment packs were supplied to each ambulance service in a central location, and were distributed from there to participating ambulance stations and vehicles. When ambulance service personnel identified an eligible patient, randomisation was achieved by opening one of the packs carried in the vehicle attending the arrest.

Post-randomisation withdrawals and exclusions

There were three main sources of post-randomisation withdrawal and exclusions. The first was when, between randomisation (opening the drug pack) and administering the trial intervention, a patient was identified as ineligible. Examples of this include when a patient achieved ROSC, when a patient was confirmed to have died or when a trial exclusion became known to the ambulance clinicians before drug administration. This group would not receive vasopressor drugs in clinical practice. No follow-up data were collected on this group of patients and they were identified in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram as post-randomisation exclusions.

The second situation is when, after drug administration, it subsequently became known that the patient was ineligible for the trial. An example of this would be discovering in hospital that the cause of the cardiac arrest was anaphylaxis. This group of patients would be exposed to the vasopressor drugs in clinical practice, as it is not until after drug administration that the exclusion is discovered. This group of patients were followed up in the normal manner and included in the intention-to-treat analysis.

The third scenario is when a patient or their legal representative withdrew their consent for ongoing data collection. This group of patients were eligible for and received the trial intervention, but incomplete data were obtained on their long-term outcomes. This group of patients were included in the intention-to-treat analysis, up until the point of withdrawal. The information sheet explained the trial and the data that were collected. The consent form separated out the different data that were collected, and gave the patient the option to decline. NHS records were continually used unless the patient explicitly refused permission for this, as were tracking of the patients via NHS Digital to determine survival to 12 months post cardiac arrest.

In the rare situation in which a patient had neither consented to nor refused follow-up, they were not included in the face-to-face follow-up, but data collection from NHS records and in-hospital data sets continued.

Blinding

Methods for ensuring blinding

The packaging and the labelling of the IMP packs did not reveal which IMP was being used; therefore, the patient, attending clinicians, hospital treating team, research paramedics and trial administration team were masked to treatment allocation. Only the statistician was able to link the IMP pack number to the allocation of adrenaline or placebo.

Methods for unblinding the trial

The chief investigator retained the right to break the code for serious adverse events (SAEs) that were unexpected and suspected to be causally related to an investigational product, and that potentially required expedited reporting to regulatory authorities. The chief investigator unblinded if requested to do so by a coroner as part of a death enquiry. In exceptional circumstances, the chief investigator also considered requests for unblinding from patients or, if they lacked capacity, family members/next of kin. In this scenario, the trial statisticians made the unblinding on the chief investigator's request and the chief investigator was informed accordingly of the allocation. This occurred only if the request was made after the benefits and harms of disclosing this information to them had been discussed. Otherwise, treatment codes (IMP pack number) were broken only for the planned interim analyses of data by the statistician at the request of the DMC.

Methods for unblinding the trial: after trial completion

Requests for unblinding of treatment allocation were received (either from survivors or from the next of kin of trial participants who were deceased) after completion of the trial. When these requests were received, the PARAMEDIC2 trial office sent the enquirer (on behalf of the ambulance services) an information sheet about unblinding and a response form for completion if they wished to continue with unblinding after having read the information provided. Once a completed response form was received, requesting unblinding, the PARAMEDIC2 trial office responded, once checks had been performed to verify the case details, to confirm the treatment allocation on behalf of the ambulance services, with ambulance service contact details for further queries.

Outcome measures

Efficacy

Primary outcome

The primary outcome was survival to 30 days post cardiac arrest.

Secondary outcomes

- Survived event (sustained ROSC, with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital).
- Survival to hospital discharge (the point at which the patient is discharged from the hospital acute care unit, regardless of neurological status, outcome or destination) and to 3, 6 and 12 months.
- Neurological outcome (mRS) at hospital discharge and at 3 and 6 months [assessed at discharge using the Rankin Focused Assessment (RFA), and completed at 3 and 6 months via the simplified modified Rankin Scale questionnaire (smRSq)].
- Neurological outcomes [assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and 'Two Simple Questions'] at 3 and 6 months.
- Health-related quality of life at 3 and 6 months [assessed using the Short Form questionnaire-12 items (SF-12) and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L)].
- Cognitive outcome at 3 months [assessed using the Mini Mental State Examination (MMSE)].
- Anxiety and depression at 3 months [assessed using the Hospital Anxiety and Depression Scale (HADS)].
- Post-traumatic stress at 3 months [Post-traumatic stress disorder Checklist – Civilian Version (PCL-C).
- Hospital length of stay.
- Intensive care unit length of stay.

The outcomes defined by the Utstein convention for reporting outcomes from cardiac arrest[92] were reported.

Rationale for outcome measures

The mRS was administered at hospital discharge and at 3 and 6 months. The mRS was selected instead of the CPC as it is more sensitive to detecting mild cognitive impairment. It can be reliably extracted from medical records and is a predictor of long-term survival. There was emerging international consensus (Utstein 2012/13[93]) that the mRS should be the primary measure of neurological outcome in cardiac arrest trials. The mRS is a seven-point scale ranging from mRS 0 (no symptoms) to 6 (dead). The RFA was chosen as a framework for assessing the mRS score at discharge, as this could be completed using a variety of sources of information, such as a patient assessment, via relatives or hospital staff or using hospital notes, and has been shown to have high inter-rater reliability.[94] The smRSq[95] was used to collect the mRS score at 3 and 6 months, as this could be easily self-completed by the patient or legal representative. The spectrum of impairment of health-related quality of life following cardiac arrest includes memory and cognitive dysfunction, affective disorders and post-traumatic stress disorder (PTSD).[96] The SF-12 is a standard quality-of-life measure that is short and easy to complete.

In addition, the EuroQol-5 Dimensions (EQ-5D) questionnaire was used as a health utility measure for the health economic analysis. Cognitive function was assessed using the MMSE.[97] The IQCODE and the 'Two Simple Questions' tool[98] formed supplementary assessments of cognitive function. The PCL-C[99] is a 17-item self-administered questionnaire measuring the risk of developing PTSD and had been used in previous studies as a good surrogate for the clinical diagnosis of PTSD, which requires a face-to-face interview by a suitably trained professional. The HADS is a 14-item self-administered questionnaire that had been previously used successfully to measure affective disorders in cardiac arrest survivors.[100] Two of these measures (PCL-C and HADS) were used as part of a multicentre follow-up for people surviving a critical illness (Intensive Care Outcome Network study);[101] the people from this study were used as a reference population.

Health economics

Primary economic outcome

The primary economic outcome was the incremental cost per quality-adjusted life-year (QALY) gained with use of adrenaline compared with the incremental cost per QALY gained with use of placebo from the perspective of the NHS and Personal Social Services (PSS) over a 6-month time horizon. QALYs were calculated using area-under-the-curve methods, assuming linear interpolation between baseline utility (set to zero) and utility values derived from a combination of mRS and EQ-5D-5L assessments at hospital discharge and at 3 and 6 months post randomisation.

Secondary economic outcomes

- Incremental cost per QALY gained from the perspective of the NHS and PSS with 1-year and lifetime (via decision-analytic modelling) time horizons.
- Incremental cost per unit increase in the proportion surviving to 6 months post cardiac arrest, estimated from an NHS/PSS perspective.
- Incremental cost per unit increase in the proportion surviving with good neurological outcome at 6 months post cardiac arrest, estimated from an NHS/PSS perspective.
- Cost of critical care stay, cost of hospital stay, use of NHS and PSS resources after discharge and broader resource use after discharge. Resource use and costs were estimated over the 6-month period from randomisation/cardiac arrest event onwards.

Sample size

Incidence of primary outcome

Most existing data refer to survival to hospital discharge rather than survival to 30 days, but as most mortality will occur in the first few days after cardiac arrest, we expect these two measures to be very similar. Estimates of long-term survival of patients who receive adrenaline during a resuscitation attempt vary between about 3.5% and 12%. From national data for England, overall survival to hospital discharge of patients for whom resuscitation is attempted is 7%.[89] However, this will include a small number of patients who achieve ROSC immediately and would not receive adrenaline, and hence would not be recruited to the trial. As these patients have much better outcomes, we expected that the survival among the trial population would be slightly lower. Estimates from the Norwegian trial of i.v. drugs and the Australian trial of adrenaline were 9%[57] and 4%,[56] respectively. We therefore expected a rate of survival to 30 days of $\approx$ 6% in the adrenaline group.

The trial's primary aim was to estimate the treatment effect of adrenaline and the uncertainty around this; we therefore based the target sample size primarily on the precision of the estimate of the risk ratio (RR).[40] *Figure 5* shows the precision that is achievable (width of the 95% CI for the RR) with different total sample sizes, for RRs (placebo vs. adrenaline) of 1.25 and 1.00. A RR of 1.25 corresponds to an increase in 30-day survival from 6% in the adrenaline group to 7.5% in the placebo group.

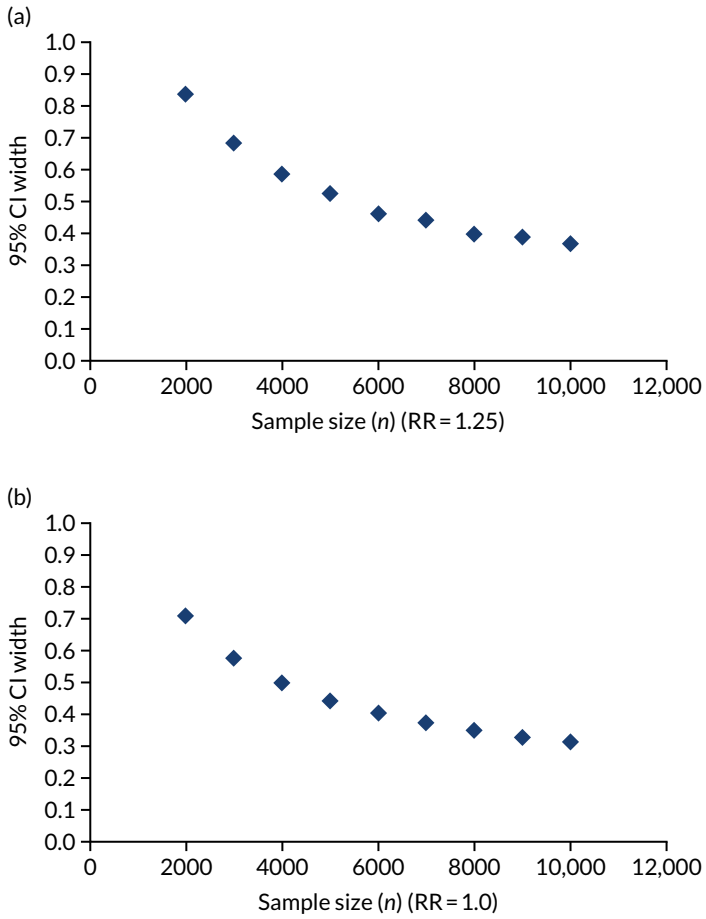

FIGURE 5 Width of 95% CI for the RR against sample size. (a) RR 1.25; and (b) RR 1.0, with 6% survival in the adrenaline arm.

Sample size

The target sample size was 8000 participants, which was expected to give a width of the 95% CI for the RR of approximately 0.4 or slightly less; for a RR of 1.25, the 95% CI would be 1.07 to 1.46, and for a RR of 1.0 the 95% CI would be 0.84 to 1.19. There was a trade-off between precision and practicality in setting a target sample size at > 8000, there was only a small improvement in precision, but the difficulty and time needed to recruit this number increased significantly. We expected a very small number of missing data for survival outcomes. In the PaRAMeDIC trial,[102] we ascertained survival status for > 99% of randomised patients; therefore, we have not adjusted the sample size estimates to account for missing data.

Using a conventional sample size calculation based on a significance test, a sample size of 8000 would have 93% power to achieve a statistically significant ($p < 0.05$) result if the true treatment difference is a RR of 1.33 (increase from 6% in the adrenaline group to 8% in the placebo group), or 75% power if the true treatment difference is a RR of 1.25 (increase from 6% in the adrenaline group to 7.5% in the placebo group).

Reconsideration of sample size after low survival rate

In July 2016, the DMC raised concerns regarding a lower than anticipated survival rate. We explored additional data sources and the current literature to assess if the original assumption was correct. Since the inception of the trial, we had access to two contemporary sources of information for the epidemiology and outcome of this patient group in the UK.

The first was a secondary analysis of the PaRAMeDIC trial.[102] The PaRAMeDIC trial[102] enrolled adult patients experiencing OHCA in three English and the Welsh ambulance service regions. Patients were eligible for enrolment if they had an OHCA attended by a trial vehicle and resuscitation was continued by the EMS team. Patients who were pregnant or who sustained a traumatic cardiac arrest were excluded. We collected information on whether or not a patient received i.v. cardiac arrest medications per se, rather than specifically adrenaline. As resuscitation algorithms recommend that adrenaline and amiodarone (the only other recommended i.v. drug for cardiac arrest) are given together, we believed that this was a reasonable surrogate to the patient requiring i.v. adrenaline. For the PaRAMeDIC trial,[102] this group comprised 3621 patients, with an overall 30-day survival rate of 2.8%.

The second source of data was the national OCHA registry (OHCAO) hosted by the University of Warwick.[103] This registry collects process and outcome information from all English ambulance services. Data were available covering the period from 2013 to 2015. These data were analysed for patients aged > 16 years who were given i.v. adrenaline ($n = 28,939$). In this group, 3.1% survived to discharge.

We extended the initial review of the literature to include studies that included standard-dose adrenaline as control, rather than limiting to intervention. *Table 2* gives a brief detail of these studies, together with the percentage rates for survival to discharge for patients receiving standard-dose adrenaline (1 mg). This identified 10 studies in which high-dose adrenaline or vasopressin were given as comparator. In one trial, placebo was given as comparator.[56] The median rate of survival to discharge was 2.8%, and the weighted mean was 3.5%.

TABLE 2 Studies in the current literature (1 mg of adrenaline arm presented)

Study	Number of survivors (*n*)	Participants receiving intervention (*n*)	Survival to discharge (%)	Comparator	Population	Setting	VF (%)
Brown *et al.*[104] 1992	26	632	4.1	High-dose adrenaline	Adults	OHCA	49
Callaham *et al.*[105] 1992	3	270	1.1	High-dose adrenaline	Adults	OHCA (non-trauma)	21
Gueugniaud *et al.*[106] 1998	46	1650	2.8	High-dose adrenaline	Adults	OHCA (non-trauma)	16
Sherman *et al.*[107] 1997	0	62	0.0	High-dose adrenaline	Adults	OHCA (non-trauma), on arrival ED	16
Steill *et al.*[108] 1992	2	165	1.2	High-dose adrenaline	Adults	IHCA/OHCA	43
Jacobs *et al.*[56] 2011	11	272	4.0	Placebo	Adults	OHCA	43
Ducros *et al.*[109] 2011	2	16	12.5	Vaso/Epi	Adults	Witnessed OHCA	0
Gueugniaud *et al.*[110] 2008	33	1452	2.3	Vasopressin/ epinephrine	Adults	OHCA (non-trauma)	9
Lindner *et al.*[111] 1997	3	20	15.0	Vasopressin/ epinephrine	Adults	OHCA, refractory VF	100
Ong *et al.*[112] 2012	8	353	2.3	Vasopressin/ epinephrine	Adults	ED	8
Wenzel *et al.*[113] 2004	58	597	9.7	Vasopressin/ epinephrine	Adults	OHCA (non-trauma)	41

IHCA, in-hospital cardiac arrest.

Considering this information and the survival outcomes for PARAMEDIC2 at the time of our review, we concluded, as a trial team, that our initial estimates of survival to discharge/30-day survival, as detailed in the protocol, were overly optimistic. An adjusted sample size calculation based on the collected data indicated that, if we assumed a rate of survival to 30 days of 2% in the control arm, we would need > 24,000 patients for a RR of 1.33 at 90% power.

In addition, we estimated treatment effects detected by the sample size of 8000, as seen in *Table 3*.

We believed that revising the sample size to 24,000 was unachievable (and unaffordable) at that point in the trial.

We noted that the Jacobs *et al.*[56] trial showed an OR of 2.2 in the survival to discharge outcome, but with wide CIs (95% CI 0.7 to 6.3). Furthermore, a threshold of 1% in absolute risk reduction for outcomes has been used widely in resuscitation science as the threshold that defines the minimal clinically important difference.[114,115] We therefore believed that the trial would still yield valuable information about the safety and effectiveness of adrenaline if the observed survival rates continued to the end of the trial.

Consent

Obtaining consent

The ambulance service research teams received training on informed consent and assessing capacity, good clinical practice (GCP) guidelines, relevant legislation, and the trial-related procedures around consent.

Informing the patient about participation in the trial

For all patients who were transported to hospital for further treatment, ambulance service research teams conducted checks with local hospitals to determine whether or not a patient had survived. The first attempt to contact the patient and inform them of their enrolment in the trial was during their stay in hospital. The ambulance service research paramedics made contact with the patient as soon as practicable after the initial emergency had passed, taking the utmost care and sensitivity in doing so. Following our experience from an OHCA study of 4400 patients (PaRAMeDIC trial),[81] and from discussions with fellow researchers from the REVIVE AIRWAYS cardiac arrest study[116] and discussions with patient and public representatives, we believed that the earliest practicable time to approach patients and relatives was once the patient was discharged from the ICU and was on a hospital ward. This allowed sufficient time for the research team to be made aware of enrolment, to identify who the patient was, to check which hospital the patient was transferred to and whether or not they were still alive and to verify with the hospital team where the patient was in the hospital. Transfer to a ward indicated that the initial emergency had passed and the patient's condition had stabilised. It was also considered more likely that the patient had regained consciousness and it would avoid any confusion or additional distress of making an approach while the patient remained critically ill in intensive care.

TABLE 3 Scenarios of estimable effect size based on current trial parameters

Power (%)	Proportion on control (%)	Proportion on intervention (%)	ARR (%)	RR
80	2	2.98	0.98	1.49
90	2	3.15	1.15	1.57
93	2	3.23	1.23	1.62

ARR, absolute risk reduction.

For patients or legal representatives who did not speak English, patient information sheets and consent forms were translated into some common languages. When printed translations were not available in the required language, Language Line Services (now known as LanguageLine Solutions, Monterey, CA, USA) was used to translate the patient information sheets and consent forms for the patient or their legal representative.

Procedure for taking consent

The research paramedic assessed if the patient had capacity to consent, with advice from the hospital team. If the patient had capacity, they were provided with the information sheet explaining the trial and the options for their involvement. The patient was allowed time to consider the information provided and had the opportunity to ask questions and discuss with others. The research paramedic or hospital team then asked when the patient would like someone to come back to discuss participation further and potentially take consent. The patient could decide that it was not an appropriate time to discuss the trial or they could decide that they did not want to be involved, in which case their feelings were respected and their decision about continuing in the trial was recorded.

The consent form listed the different sorts of information that were collected. Specific consent was not sought to use the data already collected. If the patient did not want the trial team to continue to collect data about survival, or to access the patient's health records, then they indicated this on the consent form by not initialling the corresponding boxes or told the trial team verbally.

Research paramedics confirmed with the patient or legal representative their willingness to continue with the trial at each contact point.

In the event that a patient lacked capacity to consent, the research paramedic worked with the hospital team to identify a legal representative, defined as:

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

Or, if there is no such person:

- professional legal representative – a person independent of the trial, who is the doctor primarily responsible for the medical treatment provided to that adult
- a person nominated by the relevant health-care provider.

The legal representative was approached and provided with the information sheet explaining the trial and the options for their and the patient's involvement, including the need for them to give consent on behalf of the patient and complete questionnaires on behalf of the patient. The legal representative was given time to consider the information provided. The research paramedic or hospital team then asked when the legal representative would like someone to come back to discuss participation further and potentially take consent.

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

In exceptional circumstances, if consent was not obtained during the hospital stay, the patient or their legal representative was sent an invitation letter by post and written consent was taken at the 3-month follow-up visit, if the patient or legal representative agreed.

It is possible that the patient could have regained capacity by the time the 3-month visit was due. When contacting the legal representative to arrange the 3-month visit, the ambulance service research team asked if they could speak with the patient. If, on assessment of the patient, either on the telephone or at the visit, it was found that the patient still lacked capacity, the legal representative was asked to complete the questionnaires on behalf of the patient. If the patient had regained capacity, then information was provided about the trial and consent for further data collection was sought.

General information about the trial and contact details for further information was made freely available throughout the trial. Information about the trial was placed on ambulance trust and University of Warwick websites, ambulance service public newsletters, posters and information leaflets were shared with general practices, pharmacies, hospital accident and EDs and waiting areas, totalling 6500 mail-outs, which included 2356 general practices and 3181 pharmacies. Prior to the start of the trial, a press release was issued providing information about the trial. This was followed by periodic regional press releases as the trial progressed. The trial website was updated with information throughout the trial [www.warwick.ac.uk/paramedic2 (accessed 1 August 2019)], and was accessed > 178,000 times during the trial.

Although not required by the relevant regulations, the trial team developed a system to allow a patient to decline participation in the trial in the event that they sustained a cardiac arrest.

Requests not to participate were sent to and managed by the WCTU trial team. An online form could be completed on the website or the team could be contacted by telephone or e-mail. A stainless steel 'No Study' bracelet was issued to the person's home address and, with the person's permission, their home address was passed to the ambulance service to register the person's wishes by placing an address flag on dispatcher systems. Those requesting a 'No Study' bracelet were also told to tell those close to them their wishes and told that those wishes would be respected by the treating paramedics. Paramedics were trained to look for the bracelet when attending a cardiac arrest.

Enquiries regarding trial participation

The following process was introduced at the end of the trial to deal with trial participation enquiries from members of the public.

If a member of the public enquired as to whether or not their next of kin was enrolled in the PARAMEDIC2 trial, they completed a trial participation enquiry form. On receipt of a completed trial participation enquiry form, the PARAMEDIC2 trial office worked with the appropriate site to check whether or not the next of kin of the enquirer was enrolled in the PARAMEDIC2 trial. Once it was confirmed, a letter was sent from the appropriate ambulance service to confirm whether or not the enquirer's next of kin was enrolled in the trial, along with an information sheet about the trial, which included contact details for the PARAMEDIC2 trial office.

Serious adverse events

Events that were related to cardiac arrest and that were expected in patients undergoing attempted resuscitation were not reported. These included:

- death
- hospitalisation
- persistent or significant disability or incapacity
- organ failure.

All events categorised as serious [SAE/serious adverse reaction (SAR)/suspected unexpected serious adverse reaction (SUSAR)] were required to be reported to the WCTU within 24 hours of becoming aware of the event. All reports of SAEs/SARs/SUSARs were reviewed on receipt by the chief investigators

or delegated clinical members of the TMG; the main REC, the Medicines and Healthcare products Regulatory Agency (MHRA) and the sponsor were notified within 7 or 15 days of receipt of those that were considered to satisfy the criteria for being related to the IMP and unexpected, in accordance with regulatory requirements. Reports of SAEs/SARs/SUSARs were also reviewed by the DMC at its regular meetings, or more frequently if requested by the DMC chairperson.

Procedures in case of pregnancy

Known pregnancy at the time of the cardiac arrest was an exclusion criterion for this trial. However, should the patient later be known to have been pregnant at the time of cardiac arrest and trial intervention, the protocol specified that the outcome of the pregnancy would be followed up and documented, even if the subject was discontinued from the trial. All reports of congenital abnormalities or birth defects were to be reported and followed up as a SAE.

Protocol non-compliances

Any deviations from or violations of the trial protocol or GCP were reported to the WCTU trial team promptly via a paper case report form (CRF) or an electronic case report form (eCRF). Any reports were assessed by the trial team on the day of receipt, or the following working day if received on a weekend, and escalated to the chief investigator (or their delegate), the quality assurance team and the WCTU manager if the non-compliance was a new or an exceptional event. All non-compliances, including cumulative numbers, trends and frequency over time, were reviewed at monthly trial management meetings. All violations and serious breaches were reported to the sponsor, and serious breaches were reported to the MHRA within 7 days (*Figure 6*). The ambulance service trial teams put in place corrective and preventative actions to mitigate the risk, and these actions were reviewed by the WCTU trial team to ensure that all had been completed.

A protocol deviation was defined as a change or departure from the clinical trial protocol and/or GCP that did not result in harm to the trial participants or significantly affect the scientific value of the reported results of the trial.

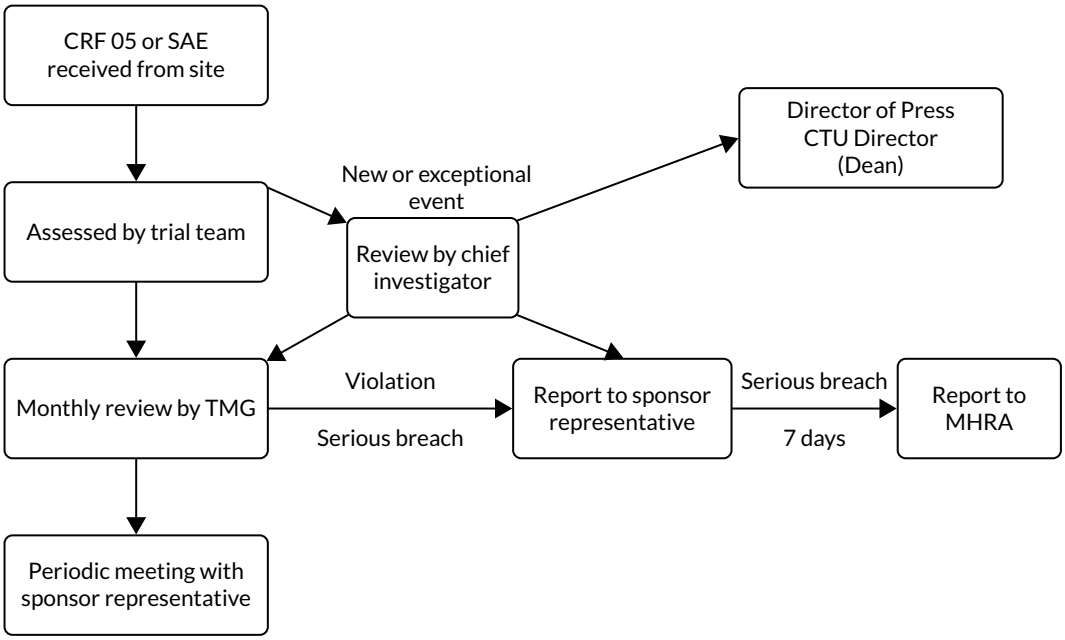

FIGURE 6 Process for receipt of a non-compliance report. CTU, Clinical Trials Unit.

A protocol violation was defined as a serious non-compliance with the approved protocol resulting from error, fraud or misconduct.

A serious breach was defined as a breach (deviation or violation) that was likely to affect, to a significant degree, either the safety or physical or mental integrity of the participants of the trial, or the scientific value of the trial.

Data collection

Screening data

Data were collected on a screening log of all cardiac arrests, which were attended by a trial-trained paramedic in the trial areas. These data consisted of the case identifier, the age and sex of the patient and the reason why the patient was not enrolled in the trial. This allowed assessment of the proportion of missed enrolments and the reasons, to ensure that the trial sample was representative of the trial population. The reasons for missed enrolments were established either from reviewing the patient's clinical record, or from speaking to the attending clinician. Several strategies were used during the trial to reinforce the message that all eligible patients should be enrolled in the trial, and data on the numbers and reasons for missed enrolments were reviewed throughout the trial and fed back to sites.

Patient enrolment

All cardiac arrests for which a trial pack was opened were reported to the ambulance service trial teams by the recruiting clinician. The method for notification of enrolled patients was specific to each research site, but was usually done via telephone to the control centre or to a dedicated telephone number. Once ambulance service research teams were notified of an enrolled patient, the patient details were registered promptly on the trial database via an online web application hosted by the University of Warwick.

Baseline cardiac arrest data

Baseline cardiac arrest data were obtained retrospectively from ambulance service clinical records and the OHCAO registry (University of Warwick) and transcribed directly onto eCRFs via the PARAMEDIC2 web application. All ambulance service staff were trained on how to collect and enter trial data, and all data definitions followed Utstein recommendations.[92] Follow-up data were then obtained from hospitals, general practitioner (GP) surgeries, NHS Personal Demographics Service and patient follow-up questionnaires and were entered into the PARAMEDIC2 web application as they became available.

Hospital

Patients were taken to any hospital in the trial regions. Although hospital clinicians did not have a role in delivering the trial interventions, they were informed about the trial and were provided with information about the trial for any clinicians or patients who needed it.

Hospitals were contacted initially to ascertain survival of patients handed over from ambulance services to the ED. If the patient had survived, the research paramedics liaised with the hospital clinicians to visit the patient and seek consent for continuation in the trial (see *Consent*).

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

Survival checks

Survival checks were completed by the ambulance service research teams or the WCTU trial team using a variety of sources:

- hospital data
- Summary Care Record/Welsh Demographic Service
- GP surgeries.

Follow-up

Survivors willing to take part were followed up approximately 3 months and 6 months after their cardiac arrest, as per *Figure 4*. Whenever possible, the 3-month assessments were a home visit, but, if the patient preferred postal questionnaires or to go through the questionnaires over the telephone, this was arranged, although the MMSE was not completed over the telephone. Questionnaires at the 6-month time point were sent by the WCTU and returned by post.

Following the approach to the patient, in the unlikely event that we had not obtained a response from the patient, the WCTU trial team approached the patient's GP or hospital or ambulance service for information on their mRS score as close to the 3- and 6-month time points as possible. If the 3-month booklet had not been completed by the time the 6-month visit was due, the patient was sent the 3-month booklet to complete instead, so that outcomes that are only collected at 3 months were not missed.

Data linkage with other data sets

Data on each patient's stay in hospital were collected retrospectively from the following electronic data sets to provide data on length of stay in hospital and hospital interventions:

- Intensive Care National Audit and Research Centre (ICNARC).
- Patient Episode Database for Wales (PEDW).
- Hospital Episode Statistics (HES).
- UK Transplant Registry (UKTR).

An application was made to receive data from the National Institute for Cardiovascular Outcomes Research data set. However, the application was not approved in time for data to be received in time for analysis.

Quality of cardiopulmonary resuscitation

Information on CPR quality is increasingly being viewed as an international reporting standard for cardiac arrest research.

The executive summary of the European Resuscitation Council Guidelines for Resuscitation 2010[88] identifies four critical components of high-quality CPR: minimise interruptions in chest compressions (as measured by chest compression fraction), provide compressions of adequate rate, provide compressions of adequate depth and allow full chest recoil between compressions.

Because a way to measure chest recoil was unavailable, the first three parameters were measured:

1. chest compression fraction, also known as chest compression ratio
2. chest compression rate
3. chest compression depth.

A preliminary review of existing literature showed that these three variables are typically studied using measurements covering two time periods:

1. initial 5 minutes of recorded CPR treatment
2. whole episode of recorded CPR treatment.

To measure these indicators of the quality of CPR for PARAMEDIC2 trial cases, data were downloaded from defibrillators, when possible. Three models of defibrillators were used across two ambulance services:

- London Ambulance Service –
  - LIFEPAK® 15 monitor/defibrillator (Physio-Control, Inc., Redmond, WA, USA)
  - LIFEPAK® 1000 defibrillator (Physio-Control, Inc.).
- North East Ambulance Service –
  - X Series® monitor/defibrillator (ZOLL Medical Corporation, Chelmsford, MA, USA).

When it was not possible to download quality of CPR data using existing means, a CPR card was used as a substitute. These Conformité Européenne-marked CPR cards, supplied by Laerdal Medical (Stavanger, Norway), measured compression fraction, compression rate and depth. CPR cards were operated by being switched on and placed centrally on a patient's chest. Chest compressions were then performed as usual. Quality of CPR data were recorded during the resuscitation attempt, but the card did not provide real-time feedback to the paramedics.

In total, 1000 CPR cards were distributed to South Central Ambulance Service, the Welsh Ambulance Service and the West Midlands Ambulance Service. Trial-trained paramedics were taught how to use the CPR cards. Trial sites used site-specific processes to return used CPR cards from paramedics to site research teams. Site research teams downloaded data from the returned used CPR cards and provided the quality of CPR data securely to the WCTU. Data from both the defibrillators and CPR cards were entered into the trial database for analysis.

Table 4 compares the feasibility of acquiring the needed parameters and measurement periods from the devices used for the PARAMEDIC2 trial. The X Series defibrillator records all three parameters;

TABLE 4 Parameters and measurement periods feasible for devices used to acquire data indicating the quality of CPR treatment during the PARAMEDIC2 trial

		Device		
Parameter	**Period**	**CPR cards (Laerdal Medical) (SCAS, WAST and WMAS)**	**LIFEPAK 15 and LIFEPAK 1000 defibrillators (Physio-Control, Inc.) (LAS)**	**X Series defibrillator (ZOLL Medical Corporation) (NEAS)**
Compression depth	1-minute intervals	Not feasible	Not feasible	Feasible
	Whole episode	Feasible	Not feasible	Feasible
Compression rate	1-minute intervals	Not feasible	Feasible	Feasible
	Whole episode	Feasible	Feasible	Feasible
Compression fraction or ratio	1-minute intervals	Not feasible	Feasible	Feasible
	Whole episode	Feasible	Feasible	Feasible

LAS, London Ambulance Service; NEAS, North East Ambulance Service; SCAS, South Central Ambulance Service; WAST, Welsh Ambulance Service; WMAS, West Midlands Ambulance Service.

an arithmetic mean (or average) value is given for the whole treatment episode and arithmetic mean values are also given for 1-minute intervals. The CPR cards record all three parameters, with an arithmetic mean value given for the whole treatment episode only; 1-minute intervals are not possible. The LIFEPAK 15 and LIFEPAK 1000 defibrillators record compression rate and compression fraction only (compression depth is not possible without an additional puck-sized sensor). Instead of the arithmetic mean, a 'trimmed mean' value (namely a mean that removes the extreme observations) is given by the LIFEPAK defibrillators for the whole treatment episode, and also for each 1-minute interval.

Statistical analyses

Primary and secondary outcomes

The primary analysis was performed with and without adjustment in the modified intention-to-treat population, which included all the patients who had undergone randomisation and were confirmed to have received the assigned intervention.

Other approaches, for instance per protocol and complier-average causal effect, were not considered because of the negligible proportion of non-compliance. For data with a normal distribution, means and standard deviations (SDs) are presented. For data that were non-normally distributed, medians and IQRs are presented. Categorical data are summarised as frequency and percentage.

Fixed-effect regression models were used to examine survival outcomes with and without adjustment. Variables included in adjusted analyses were age, sex, the time between the 999 call and the ambulance arriving at the scene, the time between the ambulance arriving and trial drug administration, the suspected aetiology of the cardiac arrest, the initial heart rhythm, whether or not the event was witnessed and whether or not a bystander undertook CPR.

Length-of-stay outcomes were examined by the Hodges–Lehmann[117] method, and were reported as estimated median differences with 95% CIs. When modelling the mRS, scores of 0–3 were classified as 'good' and scores of 4–6 were classified as 'poor'; that is scores of 0–3 were regarded as a 'good' outcome and scores of 4–6 were regarded as a 'poor' outcome. If the proportional odds assumption was violated in modelling the mRS, partial proportional odds models[118,119] were used. Other secondary outcomes (including quality of life and neurological and cognitive functions) were summarised by treatment arm.

Sensitivity

A sensitivity analysis was prespecified for mRS scores at discharge and at 3 and 6 months if > 10% of the data of survivors at each time point were missing. We used last observation carried forward and best- and worst-case scenarios for imputation. For the best-case scenario, missing data are considered as having no symptoms. For the worst-case scenario, missing data are considered as having severe disability in those confirmed to be alive at follow-up, and dead in those with confirmed death or missing survival status at follow-up. Post hoc sensitivity analyses were conducted for survival at 30 days, survival at hospital discharge, and survival with a good neurological outcome at discharge and at 3 and 6 months. Best-case and worst-case scenarios and multiple imputation were used.

Unadjusted and adjusted analyses were conducted for the primary and secondary outcomes, apart from the Two Simple Questions tool. Unadjusted and adjusted ORs with 95% CIs and mean differences with 95% CIs were reported for categorical and continuous outcomes, respectively. The number needed to treat and its 95% CI were calculated for survival at 30 days.

Quality of cardiopulmonary resuscitation

We used only the data on quality of CPR collected by London Ambulance Service because insufficient data were collected from the other sites. The Mann–Whitney *U*-test was used to compare treatment differences in hospital- and ICU-free survival because of their non-normal distributions.

Subgroups

Prespecified subgroup analyses included a patient's age, cause of cardiac arrest, initial cardiac rhythm, whether or not the cardiac arrest was witnessed, whether or not CPR was performed by a bystander, interval between the emergency call and ambulance arrival at the scene, interval between ambulance arrival and the trial-agent administration, and the interval between the emergency call and trial-agent administration. A *p*-value for interaction was reported in each analysis.

Reporting of analyses followed CONSORT guidelines.

Additional analyses

Interim analyses

Prior to the start of the trial, we used the Lan–DeMets,[120] O'Brien–Fleming and Pocock alpha spending methods to determine the upper and lower stopping boundaries for the primary outcome, with no adjustment in the final analysis. Interim analyses were carried out 10 times on a quarterly basis during the trial recruitment. Reports were delivered confidentially to the DMC. The DMC reviewed these results and made recommendations to the TSC about continuation of recruitment or any modification to the trial that may have been necessary.

The DMC monitored the accumulating outcome data; one of its roles was to recommend cessation of recruitment if a clear result had been reached (i.e. if either adrenaline or placebo was clearly superior). We suggested that different thresholds of evidence for early termination were adopted if adrenaline or placebo was being more effective, as it was probable that stronger evidence would be needed to change current practice (adrenaline use) if adrenaline was found to be inferior. We therefore proposed that interim analyses were conducted frequently in the early stages of the trial, so that, if adrenaline was superior, this was detected earlier. Thus, we minimised any risks to patients while producing robust evidence that will change practice if adrenaline is inferior.

The outcomes of primary interest for the interim analyses were 30-day survival and neurological status. We prepared reports for the DMC initially every 3 months. The exact schedule of interim analyses and the nature of any early-stopping rules were determined by the DMC, in discussion with the investigators, before the start of recruitment.

Bayesian analysis

To aid in interpretation, we included a Bayesian analysis for the primary outcome and for survival with a favourable neurological outcome. The Bayesian statistical analyses were performed using RStan. All other statistical analyses were performed with the use of SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

We performed unadjusted Bayesian analyses for two outcomes, 30-day survival and survival with favourable neurological outcome, to enable us to quantify the probability of treatment effects of different sizes. We modelled the adrenaline and placebo arms separately, with the outcome for each participant being a Bernoulli (0/1) variable, with treatment arm-specific probabilities of 'success'. Non-informative beta(1, 1) priors (*Figure 7*) were used for both groups, initially. We also performed a sensitivity analysis assuming more realistic, informative priors. These were beta(5, 150) for the adrenaline group (*Figure 8*), reflecting previous knowledge that survival in the adrenaline group was very unlikely to exceed 10%, and was most likely to be around 3%, and beta(2, 20) for the placebo group (*Figure 9*), because a survival rate exceeding 20% in the placebo group was very unlikely.

We calculated the 95% and 80% highest-density intervals, and, for risk differences, the probability that the treatment effect exceeded 0%, 1% and 2% (which have been suggested as representing clinically important differences).

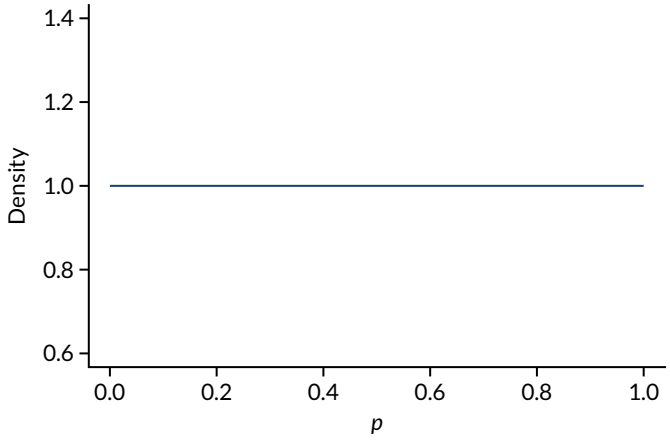

FIGURE 7 Beta(1, 1).

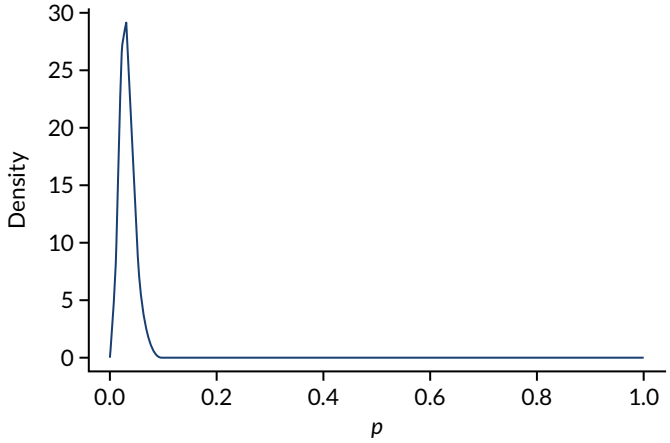

FIGURE 8 Beta(5, 150).

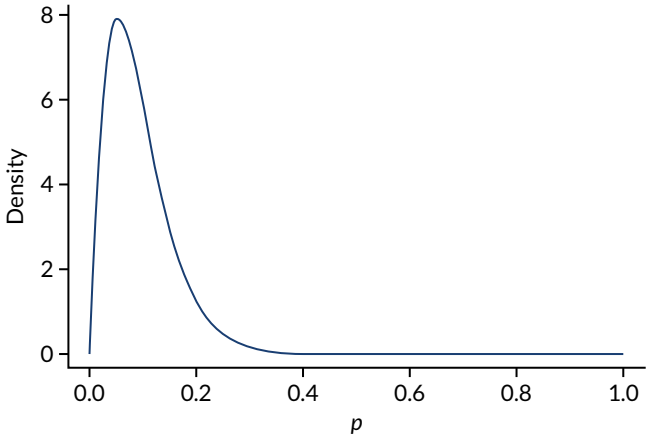

FIGURE 9 Beta(2, 20).

We present the results for the analyses of risk differences for both outcomes with the non-informative prior. The informative priors made only very minor differences to the results.

Economic evaluation

A within-trial economic evaluation and decision-analytic model that extrapolated economic outcomes beyond the trial-follow-up period were based on the trial design. The economic evaluation was conducted from the recommended NHS and PSS perspective.[121] Further details of the economic evaluation methods are presented in *Chapter 4*.

Quality control of protocol non-compliances

Protocol violations were monitored using statistical process control charts. The monthly number of violations and the proportion as a percentage of recruitment were plotted. The moving range, defined as the absolute value of month-to-month change, was plotted against the recruitment month. Any out-of-control conditions, defined as outside the prespecified limits, were investigated for quality control.

Ethics and regulatory approvals

The trial was approved by the South Central Oxford C REC (reference number 14/SC/0157) and the MHRA (EudraCT number 2014-000792-11). The trial was sponsored by the University of Warwick and was conducted in accordance with the Directive 2001/20/EC[122] of the European Parliament and of the Council of 4 April 2001 and The Medicines for Human Use (Clinical Trials) Regulations act,[123] statutory instrument 2004 No. 1031 and amendment (No. 2) statutory instrument 2006 No. 2984.

The Confidentiality Advisory Group provided approval under regulation 5 of the Health Service (Control of Patient Information) Regulations 2002[124] to process patient-identifiable information without consent (reference number 14/CAG/1009).

Several changes to the protocol and procedures were made during the trial (see *Table 1*). When these fulfilled the definition of substantial amendments according to the Medicines for Human Use (Clinical Trials) Regulations act,[123] they were reviewed and approved by the REC, the MHRA (when applicable) and ambulance trusts. Approvals were not sought at hospital level, but those trusts were notified of all amendments via the Clinical Research Network.

The funders had no role in the trial design, in the collection or analysis of the data, or in the writing of the manuscript.

Ethics considerations

In designing and conducting this trial, a number of specific ethics issues were identified that required careful consideration.

Conducting a placebo-controlled trial

As adrenaline is currently part of standard clinical treatment in cardiac arrest, a placebo controlled trial necessitates some patients not receiving standard treatment. To justify the use of a placebo in place of standard treatment, it was necessary to demonstrate that current evidence on the use of adrenaline in cardiac arrest raised sufficient doubt about its efficacy and concern about its potential harm to patients, to justify a trial that involved withholding adrenaline from some participants. There is an ethical obligation for health-care professionals to provide treatment that imparts the most benefit and least harm for the patient, based on the best available evidence. Our review of the available evidence concluded that adrenaline, as currently used, improves the rate of ROSC), but increases the likelihood of

neurological damage in those patients who survive and leave hospital. Thus, adrenaline can cause benefit and harm, and it was not clear from available evidence whether or not it caused more harm than benefit.

Given the uncertainty of the evidence, and the potential life-threatening nature of the condition being treated, it is ethically important to obtain the best evidence we can to justify treatment, while ensuring that the interests of the research participants remain paramount. Based on available evidence, the risks and benefits from participating in the trial were reasonably balanced (if a participant was randomised to placebo, they may have a reduced chance of immediate survival, but an increased chance of surviving to leave hospital neurologically intact). Our initial patient and public involvement (PPI) work suggested that members of the public value long-term survival more than short-term recovery of spontaneous circulation, so it would seem reasonable to assume that potential participants might agree to take part in a placebo-controlled trial, if they were able to do so.

Using a model of deferred consent

Enrolment in a clinical trial of a medicinal product normally requires informed consent from the participant or, if the participant lacks capacity, their legal representative. A decision about participating in a trial with potentially life or death consequences is particularly challenging, and, when treatment is not urgently required, the consent process may take considerable time. The unpredictability and immediately incapacitating nature of cardiac arrest (sudden loss of consciousness) means that it is not possible to obtain prospective informed consent from participants. Because of the need for immediate treatment, it is also not possible to obtain consent from the patient's legal representative. This situation is ethically challenging as it is not possible to respect the participant's autonomy by enabling them to make an informed choice regarding participation. The ethical justification for over-riding the usual requirement for consent must therefore be substantial with regard to the potential for the research to provide future benefit to patients or to protect them from future harm. All clinical trials of IMPs in the UK are governed by the EU Clinical Trials Directive (2001/20/EC)[122] and the Statutory Instrument 2004/1031 [The Medicines for Human Use (Clinical Trials) Regulations 2004].[123] In designing and conducting this trial, we also complied with the 2006 amendment to these regulations, relating to emergency care research that permits enrolment without consent in the emergency situation, subject to approval by an appropriate REC, and with a requirement that consent is obtained once it is no longer necessary to take action as a matter of urgency (deferred consent). Our approach was based on the template outlined at the Health Research Authority Workshop 2012 on conducting emergency research in patients who lack capacity.[125]

The ethics implications of the deferred consent model [referred to as 'exception from informed consent' (EFIC) in the USA] in relation to the constraints on the principle of respect for autonomy, and approaches to mitigate these, have been discussed in the academic literature.[126–130] Providing information to, or undertaking consultation with, the relevant population prior to the research taking place can assist in the assessment of whether or not the research is sufficiently important in terms of the clinical benefit to patients to warrant the use of deferred consent. In the initial stages of trial design, we consulted PPI members from the first PARAMEDIC trial, and held a community engagement event where the rationale of the trial was presented to 280 lay people with an interest in first aid (see *Patient and public involvement*).

Providing information prior to and during the trial also allows the opportunity for potential participants to register their wish not to participate, and for researchers to respect their autonomous prior refusal. In the USA, some RECs (Institutional Review Boards) require researchers in EFIC studies to provide a mechanism for potential participants to opt out.[131] In the UK, it is rare for trials in emergency care to provide this option. For the PARAMEDIC2 trial, we developed a substantial public communications policy and included a mechanism for members of the public to register their wish not to participate, which included provision of 'opt-out' bracelets to be worn during the trial period (see *Procedure for taking consent*).

Approaching patients or their relatives (or legal representative) to inform them about enrolment in the trial and to seek consent for continuation in the trial also required careful thought in balancing

the importance of providing information as soon as possible following the emergency and minimising distress caused by approaching relatives of patients critically ill in intensive care. Many patients lacked capacity to consent to participation in the early stages of recovery and some patients regained capacity over the period of the trial. Our consent processes were responsive to these complexities within the legal framework of the European Directive[122] (see *Procedure for taking consent*).

Informing families of patients who do not survive cardiac arrest

The sad reality of an OHCA is that fewer than 1 in 10 people survive. Experiencing the sudden unexpected loss of a loved one because of cardiac arrest is a traumatic event that frequently leads to symptoms of anxiety, depression and post-traumatic distress. Careful consideration therefore needed to be given to how, when and if the relatives of non-survivors were to be informed about participation in the trial. By the time a patient's death occurred, the trial intervention would have been implemented and no further follow-up would occur. Thus, there would be no requirement to seek consent to continue, and nor would it be useful to do so. The purpose of any communication with the family/next of kin of the deceased would be to inform them about the patient's involvement in the trial, demonstrating that the process of trial recruitment is open and transparent. In addition, it mitigates any potential harm to family members from discovering at a later date that their relative or friend had been involved in a trial without their knowledge. However, knowledge of trial participation after the event may also place a significant burden on the next of kin at a time of heightened emotional distress due to the loss of their relative or friend. Any strategy to inform the family or next of kin following a patient's death needs to balance the need for transparency with the need to minimise this distress.

The research team, including the trial ethicist, considered this issue with great care and discussed different approaches with patient representatives, clinicians caring for patients who had experienced a cardiac arrest and their families, the Resuscitation Council, and the REC. Approaches to informing the relatives of participants who do not survive can be broadly categorised as passive or active. Passive methods include placing information about the trial in publicly accessible places (e.g. websites, newsletters) and targeted sites likely to be attended by relatives of the deceased (e.g. hospitals, general practice surgeries, Registrar of Births and Deaths offices), with a contact telephone number and address for further information. This approach allows people to make a choice about whether or not and when they wish to seek further information. However, it is uncertain whether or not relatives of participants will see them. Discussion with investigators of previous UK trials in emergency of life-threatening conditions suggested that passive strategies, although not formally evaluated, had been used successfully.

Active strategies involve making direct contact with relatives through a face-to-face meeting, a telephone call or written communication. To our knowledge, this approach has not been used in previous UK OHCA trials, so we were unable to draw on relatives' or researchers' experiences of this process. There are practical barriers to providing information actively. The sudden and unpredicted nature of cardiac arrest mean that the relatives/next of kin are neither universally present nor identifiable at the time of the cardiac arrest. Information on the identity of the relatives/next of kin are also not held by ambulance services, so follow-up at a later date or time may not be possible. For people for whom resuscitation efforts are terminated in the home (≈ 40% of total cases), it is not possible for the attending paramedic to spend the necessary time to explain about the trial, answer questions and provide support to relatives who will be extremely distressed. Alternatively, providing unsolicited written information by post could exacerbate an already traumatic and stressful experience.

Having assessed the balance of benefits and burdens for relatives of the different strategies, and taking into account the importance of transparency, we concluded that the burden to families of adopting an active information strategy outweighed the potential benefits. We therefore developed a passive information strategy with a clear process for responding to enquiries from relatives of participants (and the general public) (see *Procedure for taking consent* and *Enquiries regarding trial participation*).

Patient and public involvement

During the planning and development phase, we worked with the PPI members of the PaRAMeDIC trial, who contributed to the trial design and proposed follow-up processes. Specific contributions related to the selection of outcome measures and a summary/presentation of the research in plain English. We held a community engagement event (supported by West Midlands South Comprehensive Local Research Network) in late November 2012, at which we presented the scientific rationale behind this trial to a group of 280 lay people who were interested in first aid. After preparing the talk in collaboration with one of our PPI representatives (John Long), to ensure that concepts were presented in plain, understandable English, we delivered the presentation and addressed any questions from the group. We explained the concept of short-term and longer-term outcomes and briefly sought community views about priorities for outcomes and their views on a trial of adrenaline for OHCA. We received responses from 243 participants. Ninety-five per cent of respondents indicated that long-term survival was important to them, whereas short-term survival was not. Participants broadly agreed that there was a need for further research about adrenaline as a treatment for cardiac arrest (86% agreed, 8% neither agree nor disagreed and 6% disagreed).

Prior to ethics approval for the trial being obtained, the views of the Resuscitation Council (UK) Patient Advisory Group were sought on the appropriateness of our approach to informing relatives of patients who do not survive. These views and comments supported the approach described in the protocol and ethics application.

John Long, our PPI co-applicant, with extensive experience of working with charities dedicated to reducing death from cardiac arrest, was a member of the TMG and lead PPI representative. John Long attended the REC meeting and provided important input from a patient perspective on the ethics of the trial. Since then, he has been heavily involved in TMG meetings, developing the trial procedures and processes, and reviewing public-facing information (e.g. website text and press releases) for readability and relevance. John Long has volunteered on several occasions to present the concept of the trial to several interested user groups/conferences. For example, on request by the Patient Voice Group, NHS North and West Reading Clinical Commissioning Group, John Long, one of our co-investigators and a local research fellow attended its meeting on 10 March 2015. John Long also presented the trial at several Lifesaving Foundation conferences during the trial. We also included two PPI representatives in the TSC.

In addition, the WCTU team formed a PPI group comprising eight members of the public, and chaired by John Long, to give advice on the content and distribution of patient- and public-facing documents. The group was put together through the University of Warwick's Universities/User Teaching and Research Action Partnership (UNTRAP) group and included a cross section of age, sex, religion and experience. The group have met on six occasions throughout the trial, on at least an annual basis, and have provided input on the following:

- the patient information sheet and consent forms
- process for informing patients or their relatives of their involvement in the trial
- the trial communication strategy (ways in which information about the trial can be shared in relevant communities)
- wording and layout of the trial website, trial posters, information leaflets and press releases
- issues regarding seeking/obtaining consent
- co-enrolment of participants
- end-of-trial communications, including how to communicate the results to trial participants.

Following the completion of the trial, the results were presented to the trial investigators group, and our PPI representatives were invited to attend this meeting. Here, an infographics leaflet summarising the results of the trial for patients and members of the public was presented and the PPI representatives provided feedback. Our PPI representative, John Long, also attended a Science Media Centre briefing in London to present the results of the trial to journalists and to be on hand to answer any questions from a patient or public perspective.

Chapter 3 Results

Participant flow

Recruitment took place between 23 December 2014 and 17 October 2017. The trial team assessed 10,623 patients in regions served by the London Ambulance Service NHS Trust, the West Midlands Ambulance Service University NHS Foundation Trust, the North East Ambulance Service NHS Foundation Trust, the South Central Ambulance Service NHS Foundation Trust and the Welsh Ambulance Service NHS Trust. A total of 8103 (76.3%) patients met the inclusion criteria and were randomised to the adrenaline or placebo arm by ambulance service paramedics. Within a short period of randomisation (confirming eligibility) and administration of the trial drug, 87 patients were found to be ineligible after the trial drug pack was opened, and were thus excluded post randomisation. Another two patients had an unknown allocation because of missing trial drug packs. Therefore, 4015 patients were allocated to the adrenaline arm and 3999 were allocated to the placebo arm. Details of the CONSORT flow diagram are presented in *Figure 10*. Patient flow in hospital is presented in *Figure 11*.

Losses and exclusions

Of all patients approached for the eligibility assessment, 2520 (23.7%) met the exclusion criteria. Having adrenaline before EMS' arrival was the major reason for exclusion, accounting for 1192 (47.3%) exclusions.

In practice, administration of the trial drug occurred shortly after randomisation. Within this short period, 87 patients were found to be ineligible for various reasons after the trial drug pack had been opened (see *Figure 10*). Another two patients were given the drug, but were excluded from the analysis because the drug pack number could not be verified.

After survival to hospital ward admission, patients might become lost to follow-up (LTFU) because of consent decline/withdrawal or because they were lost track of in the trial. For the primary outcome, seven patients were LTFU. A further 10 patients became LTFU within 6 months follow-up, leaving 14 and 17 with missing survival status at 3 and 6 months, respectively.

After survival to hospital ward admission, patients might become LTFU if they declined consent, withdrew consent or could not be traced by the research paramedics. Ten patients were LTFU before hospital discharge. This number cannot be compared directly with other survival outcomes measured, as the discharge time is not a fixed time point and hospital stay varied from days to months. Nine patients survived for > 30 days in hospital and died before discharge, whereas seven were discharged from hospital and later died before reaching 30 days post randomisation. In addition, six patients were LTFU in the period from 30 days to hospital discharge, and three were LTFU in the period from discharge to 30 days.

Trial participation enquiries and unblinding requests

Warwick Clinical Trials Unit received five enquiries from members of the public asking whether they or their relative had been enrolled in the trial. Of the five enquiries, two patients or their relatives were confirmed to have been enrolled.

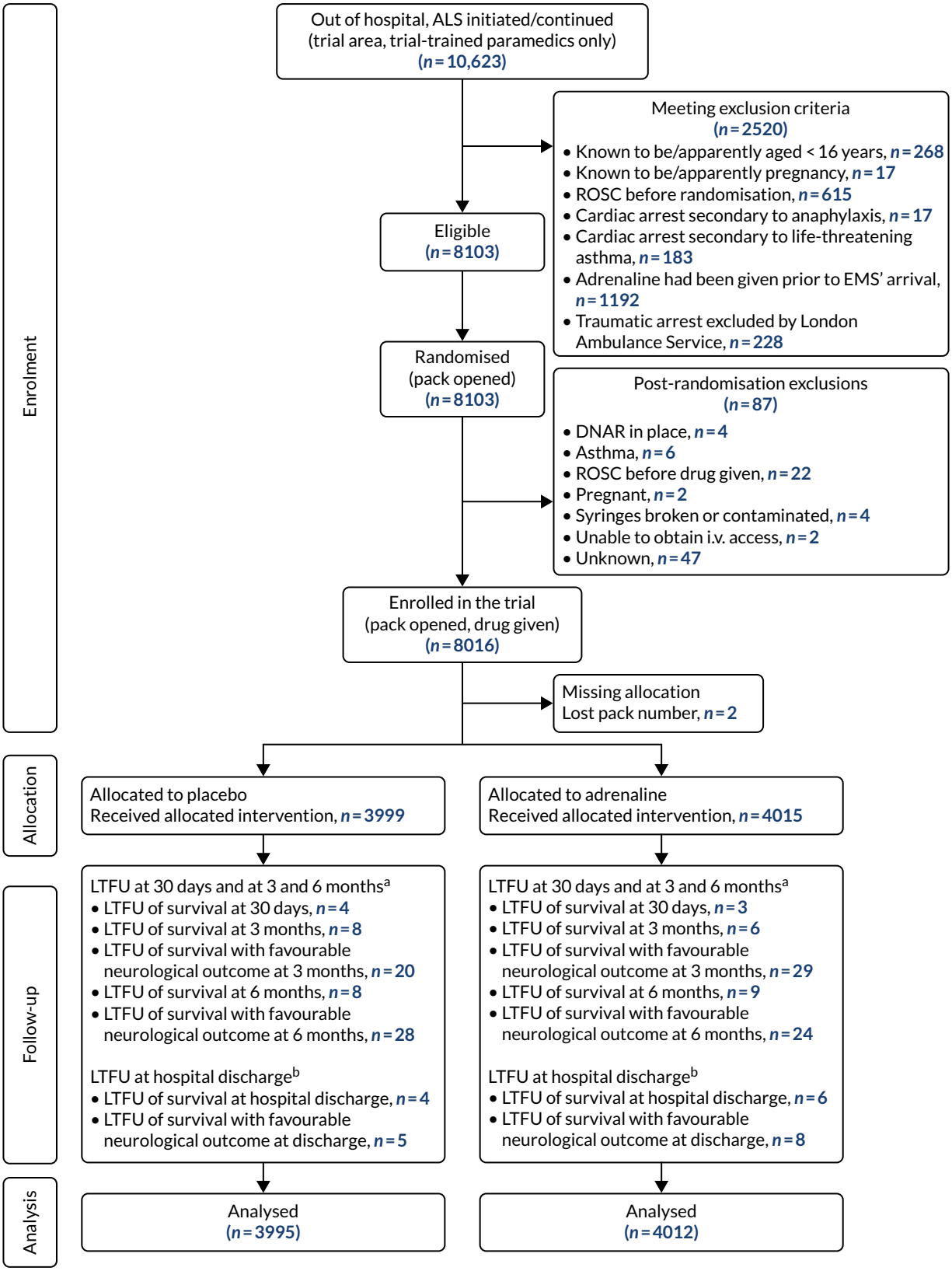

FIGURE 10 The CONSORT flow diagram. a, Cumulative loss to follow-up; b, hospital discharge was not a fixed time point, compared with the other survival outcomes and hence it was listed separately. DNAR, do not attempt resuscitation; LTFU, lost to follow-up.

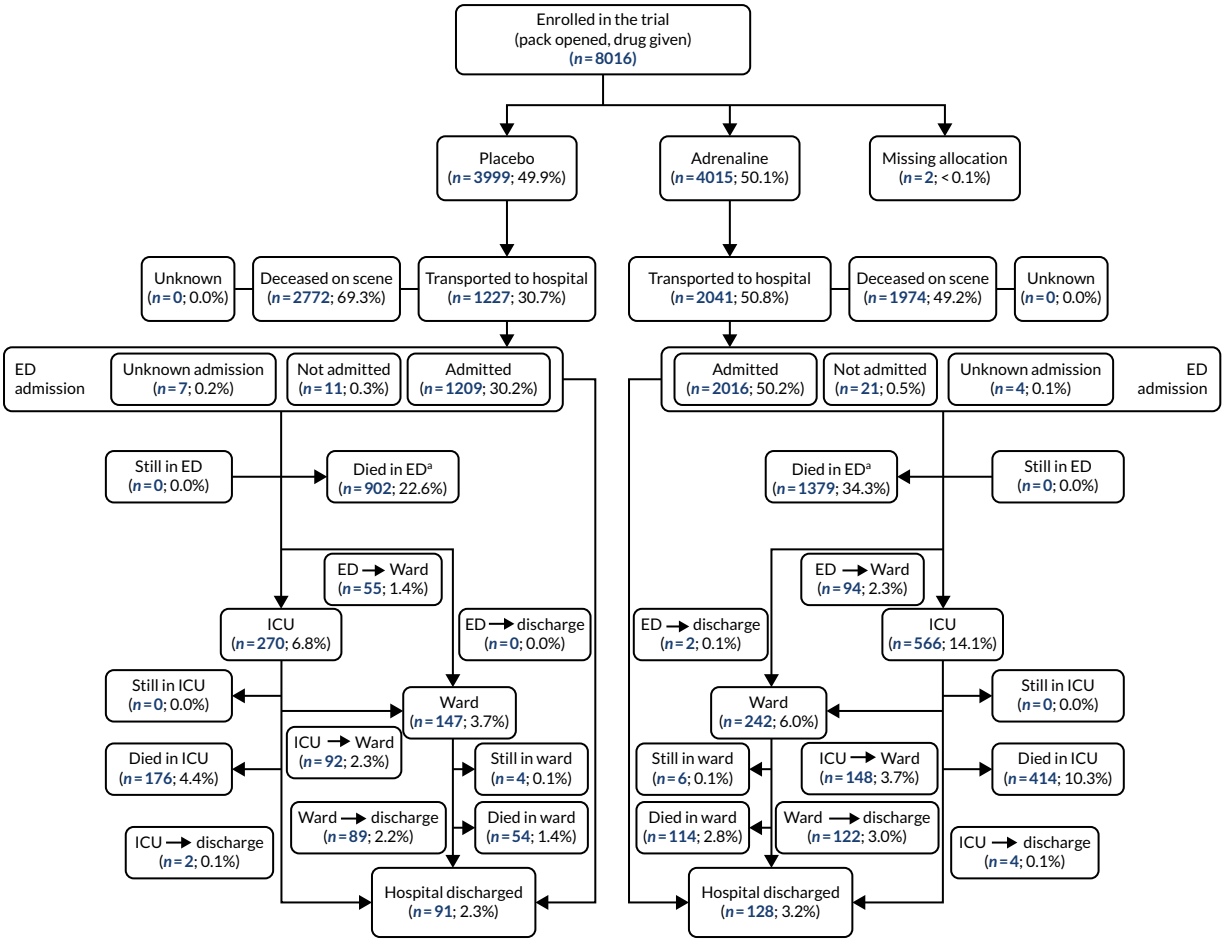

FIGURE 11 Patient flow through the trial from recruitment to hospital discharge. Note that percentages of transportation to in-hospital status are based on enrolled patients in each arm. a, A total of 213 and 391 patients are included in placebo and adrenaline boxes, respectively, as a result of unknown ICU/ward admission information.

During the recruitment phase of the trial, we received six requests for unblinding (two from HM coroners, two from relatives of deceased patients as part of complaints investigations and two as part of non-compliance investigations). In all cases, requests occurred after collection of primary outcome data. Following closure of recruitment, we received nine requests from patients or their relatives.

Overview of recruitment

Recruitment began in a staggered fashion in five ambulance services. *Figure 12* shows the cumulative recruitment at each ambulance service, as well as funder (i.e. HTA programme) targets for recruitment. The HTA programme recruitment targets were revised in July 2015 to allow a more gradual increase in recruitment, following delays in starting recruitment. *Table 5* shows the number of patients at each ambulance service who were randomised and received the trial drug (not including post-randomisation exclusions).

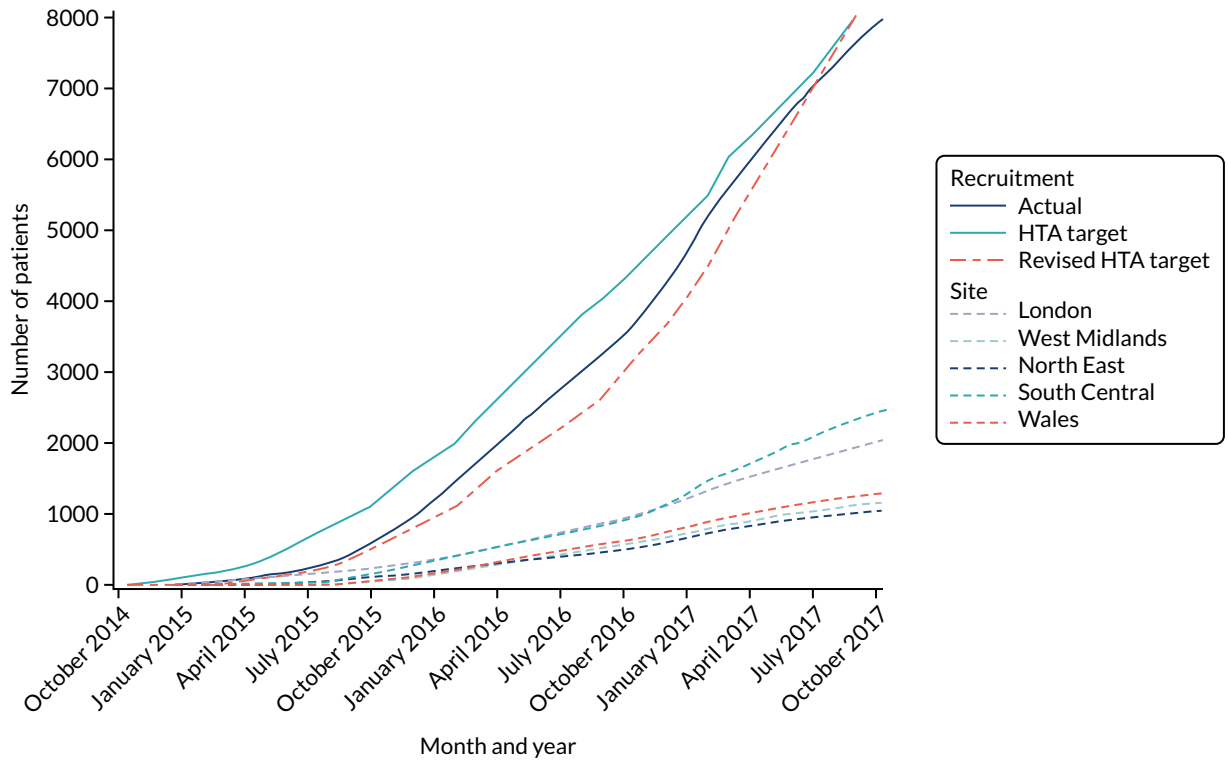

FIGURE 12 Cumulative recruitment from December 2014 to October 2017.

TABLE 5 Recruitment by region

Site	Start date	Number of recruited patients
London	23 December 2014	2058
South Central	17 February 2015	2456
North East	10 April 2015	1049
West Midlands	16 June 2015	1163
Wales	14 July 2015	1290

Baseline data

Baseline data were collected for 8016 patients. Two patients had missing allocation and were not included in the analysis. Baseline patient and event characteristics (summarised in *Tables 6* and *7*) were well balanced between the trial arms.

TABLE 6 Baseline patient and event characteristics

Characteristic	Adrenaline arm (*N* = 4015)	Placebo arm (*N* = 3999)
Age (years), mean (SD)	69.7 (16.6)	69.8 (16.4)
Sex, *n* (%)		
Male	2609 (65.0)	2584 (64.6)
Female	1406 (35.0)	1415 (35.4)
Initial rhythm, *n* (%)		
Shockable rhythm	770 (19.2)	748 (18.7)
VF	716 (17.8)	684 (17.1)
Pulseless VT	25 (0.6)	20 (0.5)
Not otherwise identified with AED	29 (0.7)	44 (1.1)
Non-shockable rhythm	3149 (78.4)	3181 (79.5)
Asystole	2135 (53.2)	2194 (54.9)
PEA/EMD	955 (23.8)	937 (23.4)
Bradycardia	20 (0.5)	16 (0.4)
Not otherwise identified with AED	39 (1.0)	34 (0.9)
Undetermined	96 (2.4)	70 (1.8)
Not identified	4 (0.1)	1 (< 0.1)
Missing	92 (2.3)	69 (1.7)
Initial aetiology, *n* (%)		
Medical (presumed cardiac)	3656 (91.1)	3691 (92.3)
Traumatic cause	66 (1.6)	57 (1.4)
Drowning	10 (0.2)	10 (0.3)
Drug overdose	74 (1.8)	72 (1.8)
Electrocution	0 (0.0)	1 (< 0.1)
Asphyxia	117 (2.9)	81 (2.0)
Not identified	1 (< 0.1)	2 (0.1)
Missing	91 (2.3)	85 (2.1)
Witness, *n* (%)		
None	1498 (37.3)	1505 (37.6)
Paramedic	452 (11.3)	470 (11.8)
Bystander	2013 (50.1)	1967 (49.2)
Not identified	1 (< 0.1)	1 (< 0.1)
Missing	51 (1.3)	56 (1.4)
Bystander commenced CPR, *n* (%)		
Bystander CPR	2382 (59.3)	2349 (58.7)
No bystander CPR	1111 (27.7)	1094 (27.4)
By paramedic during witnessed event	452 (11.3)	470 (11.8)
Not identified	1 (< 0.1)	1 (< 0.1)
Missing	69 (1.7)	84 (2.1)

EMD, electromechanical dissociation.

TABLE 7 Intervals between key events and initial response to resuscitation

	Adrenaline arm (*N* = 4015)	Placebo arm (*N* = 3999)
Time from 999 call to EMS' arrival at scene (minutes)[a,b]		
Median (IQR)	6.7 (4.3–9.7)	6.6 (4.2–9.6)
Missing, *n*	0	0
Time from 999 call to administration of drug (minutes)[a,b]		
Median (IQR)	21.5 (16.0–27.3)	21.1 (16.1–27.4)
Missing, *n*	40	50
Time from EMS' arrival at scene to leaving scene (minutes)		
Mean (SD)	50.1 (21.8)	44.5 (18.3)
Missing, *n*	1976	2773
Time from EMS leaving scene to arrival at hospital (minutes)		
Mean (SD)	12.9 (9.8)	12.4 (8.9)
Missing, *n*	1977	2774
Time from starting ALS to cessation of resuscitation efforts (minutes)[b]		
n	1027	1457
Median (IQR)	47.5 (35.1–64.0)	43.1 (33.5–56.1)
Missing, *n*	947	1315
ROSC, *n* (%)		
Yes	1457 (36.3)	468 (11.7)
No	2518 (62.7)	3492 (87.3)
Missing	40 (1.0)	39 (1.0)
Patients transported to hospital, *n* (%)		
Yes	2041 (50.8)	1227 (30.7)
No	1974 (49.2)	2772 (69.3)
Patient declared deceased by ED staff, *n* (%)		
Yes	988 (24.6)	689 (17.2)
No	614 (15.3)	290 (7.3)
Not applicable (not transported)	1974 (49.2)	2772 (69.3)
Missing	439 (10.9)	248 (6.2)

a Time from 999 call to witness time from EMS; witnessed cases were defined as 0.
b Time interval was calculated only for patients who died on scene.

Pre-hospital treatment data

The summaries of pre-hospital treatments and the quality of EMS CPR are presented in *Tables 8* and *9*, respectively.

TABLE 8 Concurrent pre-hospital treatments

Pre-hospital treatment	Adrenaline arm (*N* = 4015)	Placebo arm (*N* = 3999)
i.v. access, *n* (%)	2739 (68.2)	2763 (69.1)
Missing	5 (0.1)	3 (0.1)
Unknown	76 (1.9)	66 (1.7)
Intraosseous access, *n* (%)	1340 (33.4)	1,319 (33.0)
Missing	5 (0.1)	4 (0.1)
Unknown	76 (1.9)	64 (1.6)
Number of trial drug doses		
Mean (SD)	4.9 (2.5)	5.1 (2.3)
Unknown	7	9
Administration of amiodarone, *n* (%)	584 (14.5)	368 (9.2)
Missing	11 (0.3)	14 (0.4)
Unknown	47 (1.2)	39 (1.0)
Supraglottic airway used, *n* (%)	2844 (70.8)	2847 (71.2)
Unobtainable	5 (0.1)	3 (0.1)
Unknown	176 (4.4)	164 (4.1)
Tracheal tube used, *n* (%)	1206 (30.0)	1125 (28.1)
Missing	5 (0.1)	4 (0.1)
Unknown	167 (4.2)	157 (3.9)
Number of shocks after randomisation (*n*)	3980	3962
Mean (SD)	1.4 (3.0)	0.9 (2.4)
Compression rate in the first 5 minutes (per minute)[a] (*n*)	149	137
Mean (SD)	106.8 (14.4)	106.5 (13.3)
Compression fraction in the first 5 minutes (%)[b] (*n*)	149	137
Mean (SD)	76.2 (11.2)	78.4 (13.0)

a Compression rate is derived by including only compressions in the periods of uninterrupted compression (no pause or a pause of < 3 seconds).
b Compression fraction is defined as the proportion of time of uninterrupted chest compression.

TABLE 9 Quality of EMS CPR

	Trial arm, mean (SD)	
Quality of CPR	Adrenaline (*n* = 149)	Placebo (*n* = 137)
Compression rate in the first 5 minutes (per minute)[a]	106.8 (14.4)	106.5 (13.3)
Compression fraction in the first 5 minutes (%)[b]	76.2 (11.2)	78.4 (13.0)

a Compression rate is derived by including only compressions in the periods of uninterrupted compression (no pause or a pause of < 3 seconds).
b Compression fraction is defined as the proportion of time of uninterrupted chest compression.

Numbers of patients analysed

The number analysed for each outcome is listed in *Table 10*.

Outcomes and estimations

Short- to medium-term outcomes are presented in *Table 11*. The survival rate at 30 days post randomisation was significantly higher in the adrenaline arm than in the placebo arm. The treatment difference of survival rate then decreased over time. Fewer patients who survived had a favourable neurological outcome, and differences between groups were smaller than for survival alone [0.3% (95% CI −0.3% to 0.9%) difference at discharge; 0.5% (95% CI −0.1% to 1.1%) difference at 3 and 6 months]. The number of patients with an unknown neurological outcome increased from discharge ($n = 13$) to 3 months ($n = 49$) and to 6 months ($n = 51$).

Intensive care unit- and hospital-free survival are summarised in *Figures 13* and *14*, respectively.

TABLE 10 Number analysed for primary and secondary outcomes

Outcome	Number analysed
Survival at 30 days	8007
Survival until hospital admission	7955
Survival to hospital discharge	8002
Survival at 3 months	8000
Survival at 6 months	7997
Survival at 12 months	7997
mRS at hospital discharge	8001
mRS at 3 months	7965
mRS at 6 months	7963
IQCODE at 3 months	132
IQCODE at 6 months	121
Two Simple Questions at 3 months	154
Two Simple Questions at 6 months	126
EQ-5D-5L at 3 months	154
EQ-5D-5L at 6 months	126
SF-12 at 3 months	137
SF-12 at 6 months	116
MMSE at 3 months	123
HADS (anxiety) at 3 months	144
HADS (depression) at 3 months	142
Post-traumatic stress at 3 months	137
Hospital length of stay (discharged)	218
Hospital length of stay (deceased)	7785
Intensive care length of stay (discharged)	238
Intensive care length of stay (deceased)	590
Free of hospital stay	8000
Free of intensive care	7999

TABLE 11 Results of survival, hospital stay and mRS outcomes

Outcome	Adrenaline arm	Placebo arm	Difference (95% CI)	OR (95% CI)	
				Unadjusted	Adjusted
Survival					
Primary outcome, n/N *(%)*					
30-day survival status	130/4012 (3.2)	94/3995 (2.4)	0.9% (0.2% to 1.6%)	1.39 (1.06 to 1.82)	1.47 (1.09 to 1.97)
Secondary outcomes, n/N *(%)*					
Survived to hospital admission[a]	947/3973 (23.8)	319/3982 (8.0)	15.8% (14.3% to 17.4%)	3.59 (3.14 to 4.12)	3.83 (3.30 to 4.43)
Survived to hospital discharge	128/4009 (3.2)	91/3995 (2.3)	0.9% (0.2% to 1.6%)	1.41 (1.08 to 1.86)	1.48 (1.10 to 2.00)
Survived at 3 months	121/4009 (3.0)	86/3991 (2.2)	0.9% (0.2% to 1.6%)	1.41 (1.07 to 1.87)	1.47 (1.08 to 2.00)
Survived at 6 months	117/4006 (2.9)	85/3991 (2.1)	0.8% (0.1% to 1.5%)	1.38 (1.04 to 1.83)	1.43 (1.05 to 1.96)
Survived at 12 months	107/4006 (2.7)	80/3991 (2.0)	0.7% (0.0% to 1.3%)	1.34 (1.00 to 1.80)	1.38 (1.00 to 1.92)
Hospital stay, median (IQR)					
ICU length of stay of survivors	7.5 (3.0–15.0)	7.0 (3.5–12.5)	0.0 (–1.0 to 2.0)	–	–
ICU length of stay of deceased[b]	2.0 (1.0–5.0)	3.0 (1.0–5.0)	0 (0 to 0)		
Hospital length of stay of survivors	21.0 (10.0–41.0)	20.0 (9.0–38)	1.0 (–3.0 to 6.0)	–	–
Hospital length of stay of deceased[b]	0 (0–0)	0 (0–0)	0 (0 to 0)		

continued

TABLE 11 Results of survival, hospital stay and mRS outcomes (*continued*)

Outcome	Adrenaline arm	Placebo arm	Difference (95% CI)	OR (95% CI)	
				Unadjusted	Adjusted
mRS					
Secondary outcomes					
Neurological outcome (mRS) at hospital discharge,[c] n (%)					
0 – No symptoms	12 (0.3)	15 (0.4)	–	0.80 (0.37 to 1.70)	0.80 (0.36 to 1.77)
1 – No significant disability	17 (0.4)	10 (0.3)	–	1.16 (0.68 to 1.98)	1.16 (0.66 to 2.03)
2 – Slight disability	23 (0.6)	29 (0.7)	–	0.96 (0.65 to 1.41)	0.98 (0.65 to 1.48)
3 – Moderate disability	35 (0.9)	20 (0.5)	–	1.18 (0.86 to 1.61)	1.23 (0.88 to 1.73)
4 – Moderately severe disability	12 (0.3)	8 (0.2)	–	1.21 (0.90 to 1.63)	1.26 (0.91 to 1.75)
5 – Severe disability	27 (0.7)	8 (0.2)	–	1.41 (1.07 to 1.85)	1.51 (1.12 to 2.04)
6 – Dead	3881 (96.7)	3904 (97.6)	–	1	1
Unknown	8 (0.2)	5 (0.1)	–		
Favourable neurological outcome at hospital discharge (0–3 vs. 4–6), *n*/*N* (%)	87/4007 (2.2)	74/3994 (1.9)	0.3% (–0.3% to 0.9%)	1.18 (0.86 to 1.61)	1.19 (0.85 to 1.68)
Neurological outcome (mRS) at 3 months,[c] n (%)					
0 – No symptoms	20 (0.5)	20 (0.5)	–	1.33 (0.98 to 1.80)	1.20 (0.62 to 2.33)
1 – No significant disability	30 (0.7)	20 (0.5)	–		1.39 (0.89 to 2.18)
2 – Slight disability	10 (0.2)	11 (0.3)	–		1.27 (0.84 to 1.90)
3 – Moderate disability	22 (0.5)	12 (0.3)	–		1.41 (0.99 to 2.02)
4 – Moderately severe disability	6 (0.1)	5 (0.1)	–		1.41 (0.99 to 1.99)
5 – Severe disability	10 (0.2)	6 (0.2)	–		1.45 (1.04 to 2.02)
6 – Dead	3888 (96.8)	3905 (97.6)	–		1
Unknown	29 (0.7)	20 (0.5)	–		
Favourable neurological outcome at 3 months (0–3 vs. 4–6), *n*/*N* (%)	82/3986 (2.1)	63/3979 (1.6)	0.5% (–0.1% to 1.1%)		1.39 (0.97 to 2.01)

Outcome	Adrenaline arm	Placebo arm	Difference (95% CI)	OR (95% CI)	
				Unadjusted	Adjusted
Neurological outcome (mRS) at 6 months, [c] **n *(%)***					
0 – No symptoms	25 (0.6)	19 (0.5)	–	1.51 (1.11 to 2.06)	1.38 (0.73 to 2.62)
1 – No significant disability	22 (0.5)	13 (0.3)	–		1.63 (1.01 to 2.65)
2 – Slight disability	10 (0.2)	9 (0.2)	–		1.47 (0.95 to 2.26)
3 – Moderate disability	21 (0.5)	17 (0.4)	–		1.40 (0.96 to 2.03)
4 – Moderately severe disability	7 (0.2)	2 (0.1)	–		1.49 (1.04 to 2.15)
5 – Severe disability	16 (0.4)	7 (0.2)	–		1.62 (1.15 to 2.28)
6 – Dead	3889 (96.9)	3906 (97.7)	–		1
Unknown	25 (0.6)	26 (0.7)	–		
Favourable neurological outcome at 6 months (0–3 vs. 4–6), *n*/*N* (%)	78/3990 (2.0)	58/3973 (1.5)	0.5% (–0.1% to 1.1%)	1.35 (0.96 to 1.90)	1.35 (0.93 to 1.97)

a Survival to hospital admission was defined as a sustained ROSC until admission and transfer of care to medical staff at the receiving hospital.
b Hospital length of stay for deceased included all patients who died before hospital discharge; ICU length of stay for deceased included patients who were admitted to and died in ICU. Unknown cases are not used in the difference or OR calculation. Adjustment covariates include age, sex, time from 999 call to arrival at scene, time from arrival at scene to drug administration, initial rhythm, aetiology, who witnessed the arrest and bystander CPR. All treatment comparisons are made by comparing treatment adrenaline with treatment placebo.
c Proportional odds assumption was valid only in the 3- and 6-month unadjusted mRS models. The 95% CIs have not been adjusted for multiplicity; therefore, inferences based on the intervals may not be reproducible. In total, nine patients died and six were LTFU from 30 days to hospital discharge, and seven patients died and three patients were LTFU from discharge to 30 days.

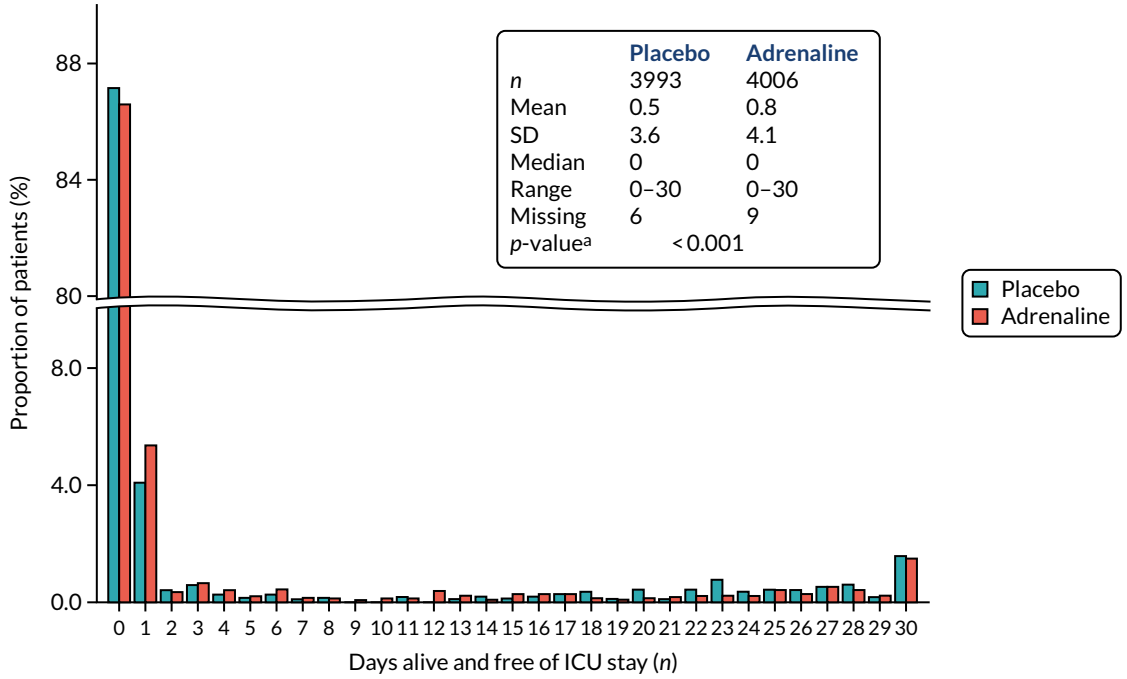

FIGURE 13 Intensive care unit-free survival (days) in the 30 days post randomisation, by treatment arm. a, Mann–Whitney *U*-test was used.

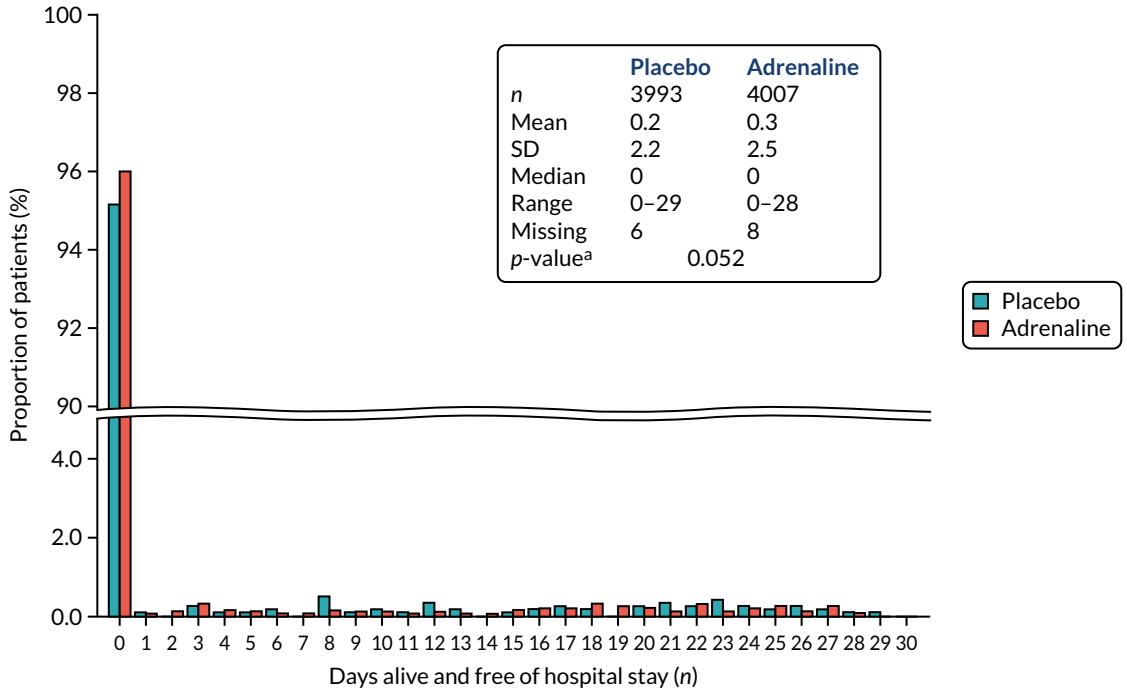

FIGURE 14 Hospital-free survival (days) in the 30 days post randomisation, by trial arm. a, Mann–Whitney *U*-test was used.

Longer-term neurocognitive and health-related quality-of-life outcomes among surviving patients are presented in *Figures 15–17*. *Figure 15* summarises outcomes whereby a higher score is better. *Figure 16* summarises outcomes whereby a lower score indicates a better health outcome. *Figure 17* presents responses to Two Simple Questions relating to requirement for assistance and mental recovery after cardiac arrest.

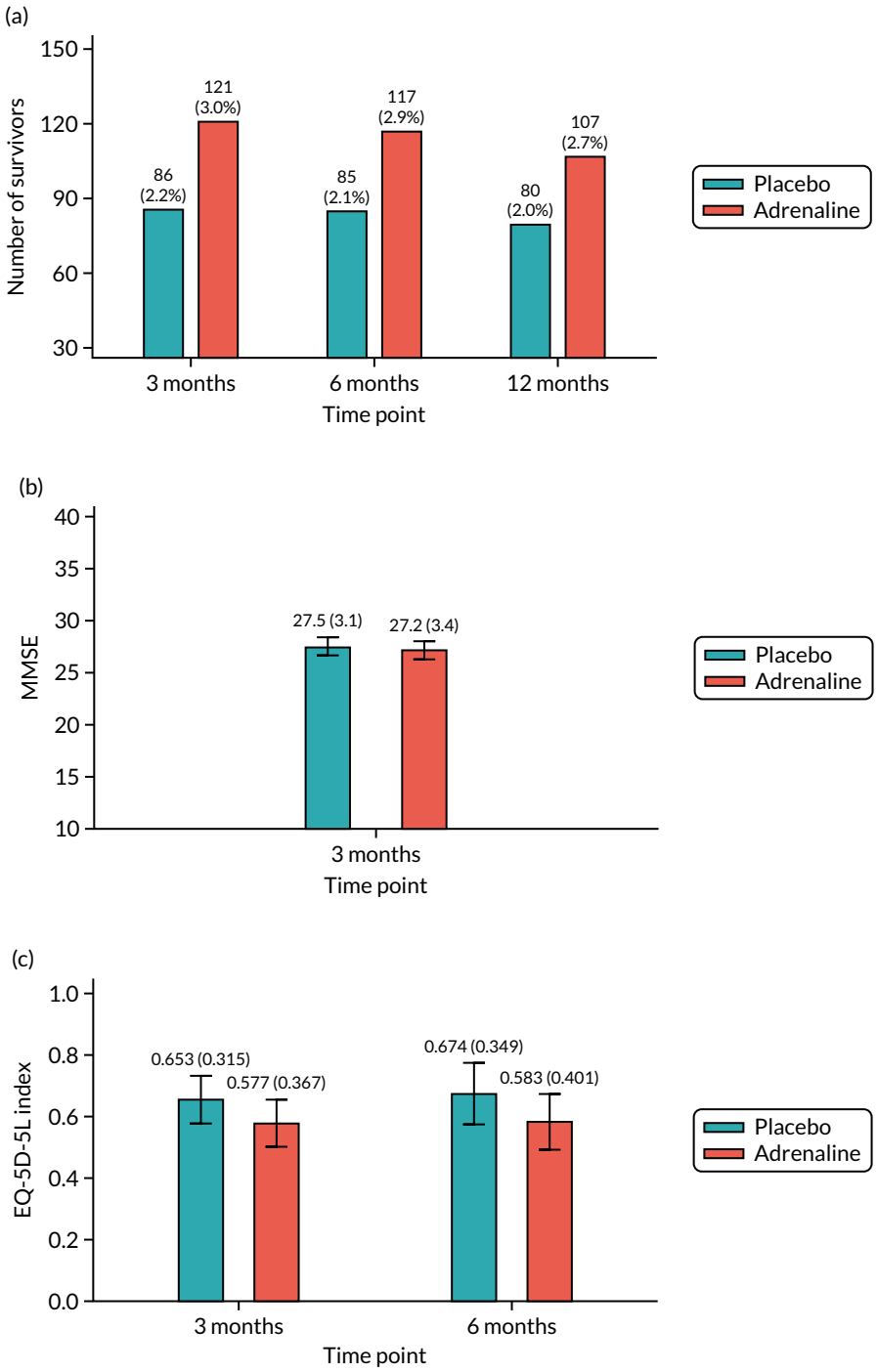

FIGURE 15 Summary of longer-term neurocognitive and health-related quality-of-life outcomes for the MMSE, the EQ-5D-5L and the SF-12 physical and mental health components. (a) Number of survivors; (b) mean (SD) MMSE score; (c) mean (SD) EQ-5D-5L score; (d) mean (SD) EQ-VAS score; (e) mean (SD) SF-12 physical health score; and (f) mean (SD) SF-12 mental health score. VAS, visual analogue scale. Note that error bars are ± 95% CIs of means. Frequency (rate) and mean (SD) are shown on top of the bars for categorical and continuous outcomes, respectively. Normal range or value of the outcomes: MMSE, 25–30 (122); HADS, 0–7 (123). The population mean is 50 (SD 10) for SF-12 and 0.86 (SD 0.23) for EQ-5D-5L index score. VAS, visual analogue scale. (*continued*)

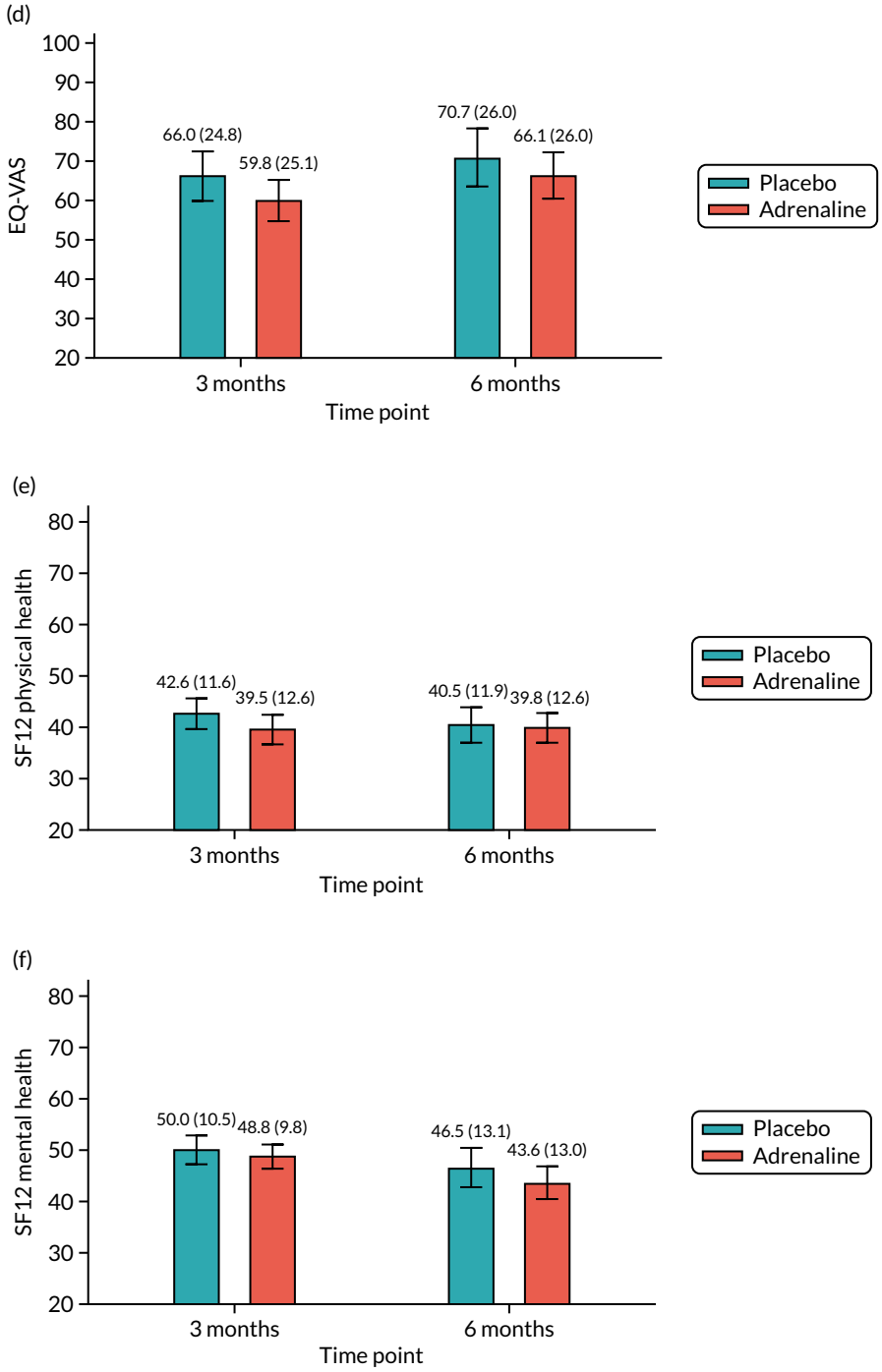

FIGURE 15 Summary of longer-term neurocognitive and health-related quality-of-life outcomes for the MMSE, the EQ-5D-5L and the SF-12 physical and mental health components. (a) Number of survivors; (b) mean (SD) MMSE score; (c) mean (SD) EQ-5D-5L score; (d) mean (SD) EQ-VAS score; (e) mean (SD) SF-12 physical health score; and (f) mean (SD) SF-12 mental health score. VAS, visual analogue scale. Note that error bars are ± 95% CIs of means. Frequency (rate) and mean (SD) are shown on top of the bars for categorical and continuous outcomes, respectively. Normal range or value of the outcomes: MMSE, 25–30 (122); HADS, 0–7 (123). The population mean is 50 (SD 10) for SF-12 and 0.86 (SD 0.23) for EQ-5D-5L index score. VAS, visual analogue scale.

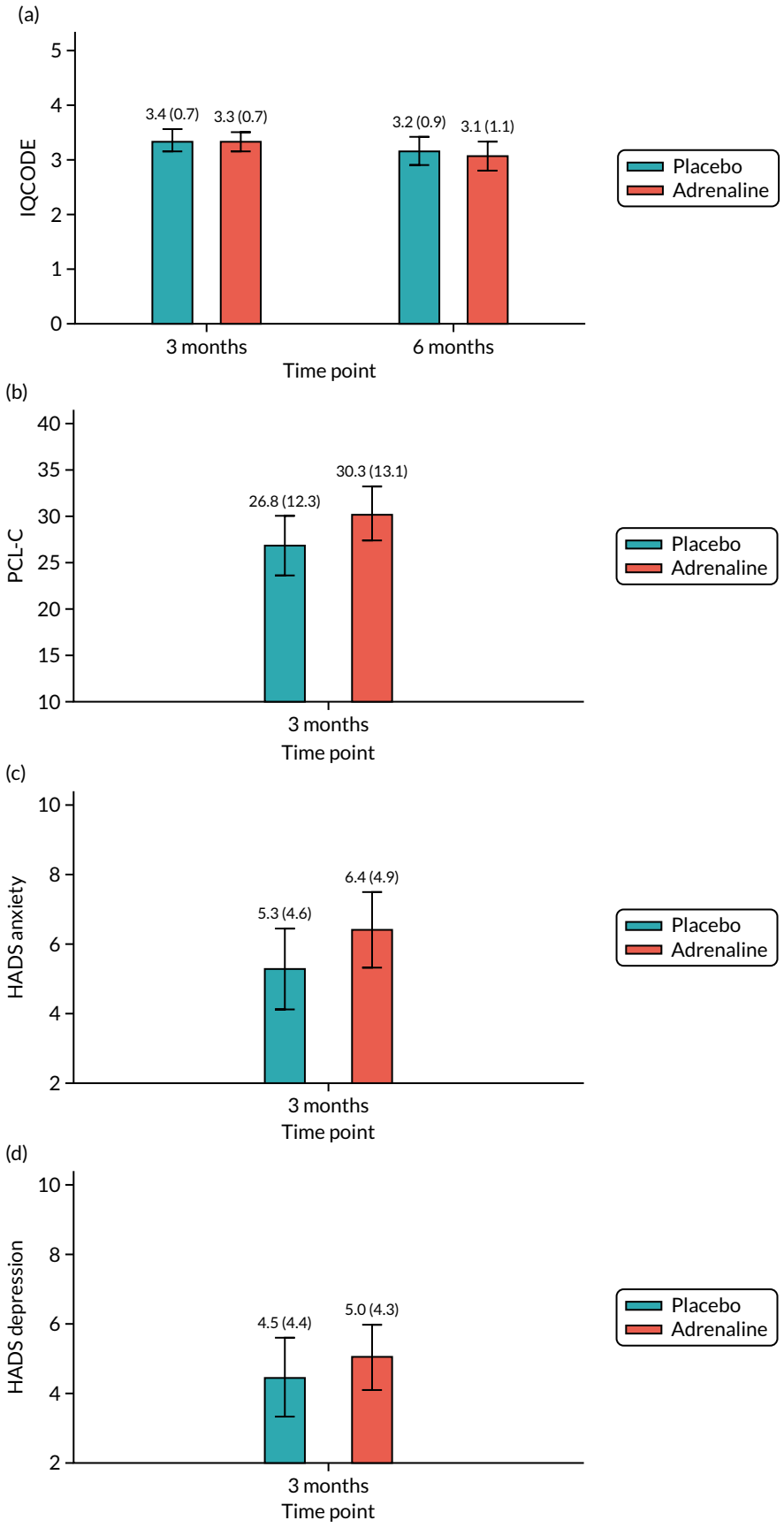

FIGURE 16 Summary of longer-term neurocognitive and health-related quality of life for (a) IQCODE; (b) PCL-C; (c) HADS anxiety; and (d) HADS depression. Note that error bars are ± 95% CIs of means. Frequency (rate) and mean (SD) are shown on top of the bars for categorical and continuous outcomes, respectively. Normal range or value of the outcomes: PCL-C, no optimal range; IQCODE, < 3.04 (124).

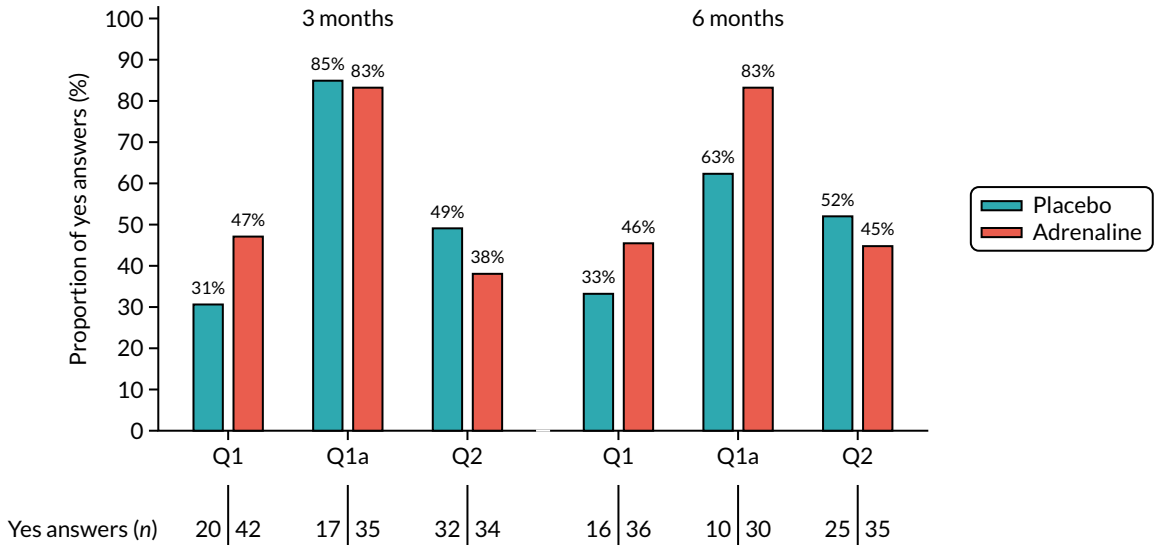

FIGURE 17 Summary of Two Simple Questions. Q1: In the last 2 weeks, did you require help from another person for your everyday activities? Q1a: If yes, is this a new situation following your cardiac arrest? Q2: Do you feel that you have made a complete mental recovery from your cardiac arrest? The Q1 and Q2 bars show the proportion of yes answers among all followed-up patients at 3 and 6 months. The Q1a bars show the proportion of patients giving a yes answer of those who answered yes to Q1. Q, question.

Ancillary analysis

Subgroup analysis

The treatment effect on survival to 30 days was further assessed in the prespecified subgroups. Survival rate was consistently higher in the adrenaline arm, but the results indicated no evidence of significant treatment difference across subgroups in both unadjusted (*Figure 18*) and adjusted analyses (*Figures 19*) (interaction $p > 0.05$).

Data linkage

Patients who survived on the scene and were transported to hospital were included for data linkage (*Figure 20*). Data linkage to HES, the PEDW, the ICNARC data set and the UKTR was conducted for the health economic analysis. The overall match rate of the ICNARC data set and the UKTR are 22.9% and 5.5%, respectively.

The linkage rates for the HES data sets are 96.4% for the PEWD (Welsh HES), 82.1% for NHS Digital and 92.2% across both data sets.

Sensitivity analysis

Four scenarios were evaluated in the analysis, including best-case scenario in both arms (A), worst-case scenario in both arms (B), best-case scenario in the placebo arm and worst-case scenario in the adrenaline arm (C), best-case scenario in the adrenaline arm and worst-case scenario in the placebo arm (D), and multiple imputation assuming missing at random (E). Best cases were defined as patients surviving and worst cases were defined as patients dying. Results were presented in *Table 12*. The longer-term outcomes are more affected by the individual imputation scenarios (C and D), but the majority of the results, including those of the multiple imputation approach, were in line with the main results.

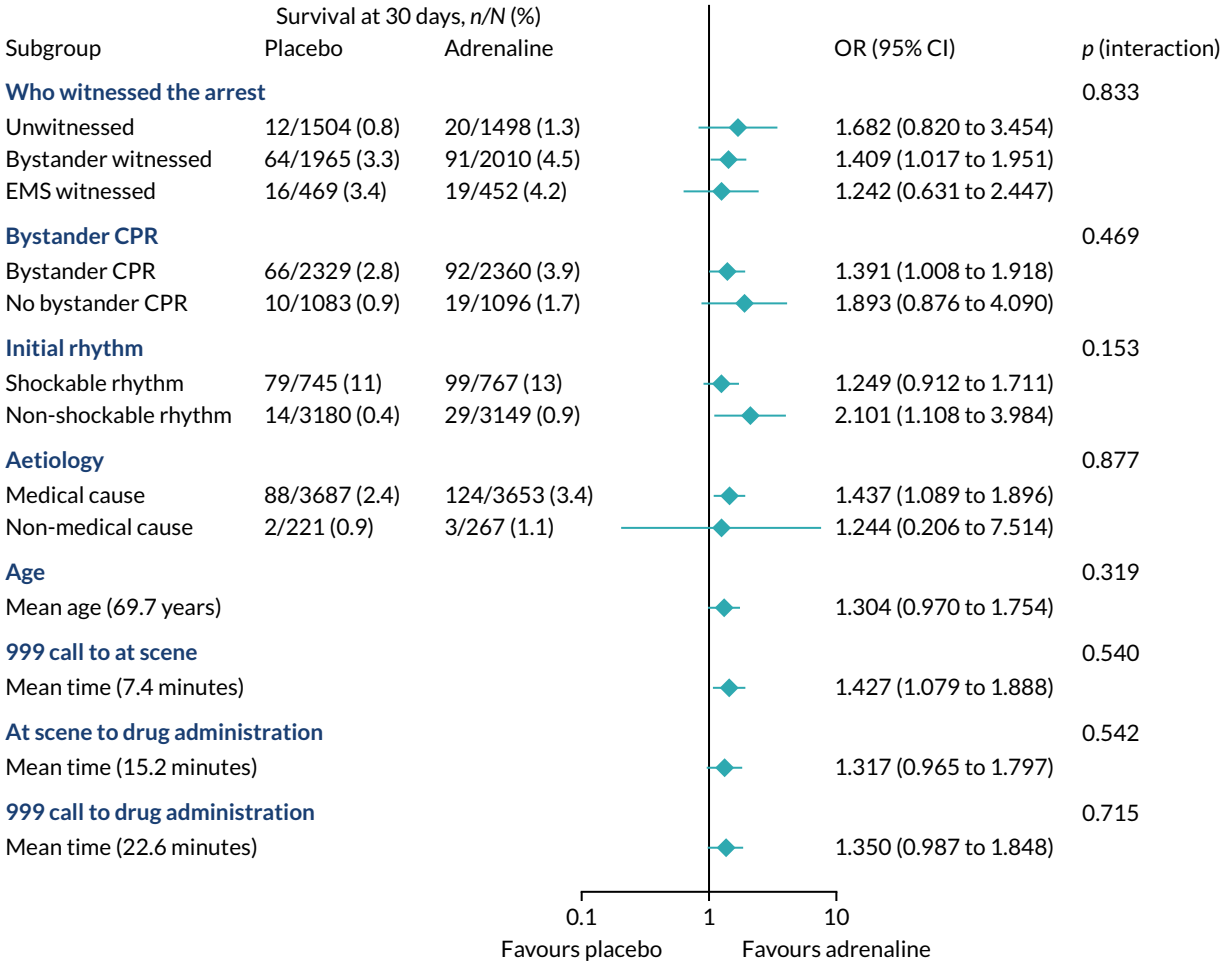

FIGURE 18 Unadjusted subgroup analysis.

Harms, serious adverse events

Serious adverse events

No events fulfilling the criteria for SAEs, SARs or SUSARs were reported during the trial.

Protocol deviations and violations

Table 13 shows the type and frequency of protocol deviations and violations throughout the trial, and *Figure 21* shows the number of violations over time as a proportion of recruitment in each month. Overall, the proportions were small. The peak in October 2015 was mainly as a result of the small number of participants recruited by this early stage. The dotted line shows the decreasing trend of violations over time. *Figure 22* is the statistical process control chart of the change of protocol violations over time, as a percentage of recruitment, from June 2015 to October 2017. The violation had large variation at the early stage, due to the peak in October 2015 (see *Figure 22*). The change then stabilised and was mostly limited to the upper one-sigma (SD) limit.

Serious breaches

Two serious breaches occurred during the trial, as outlined in the following sections.

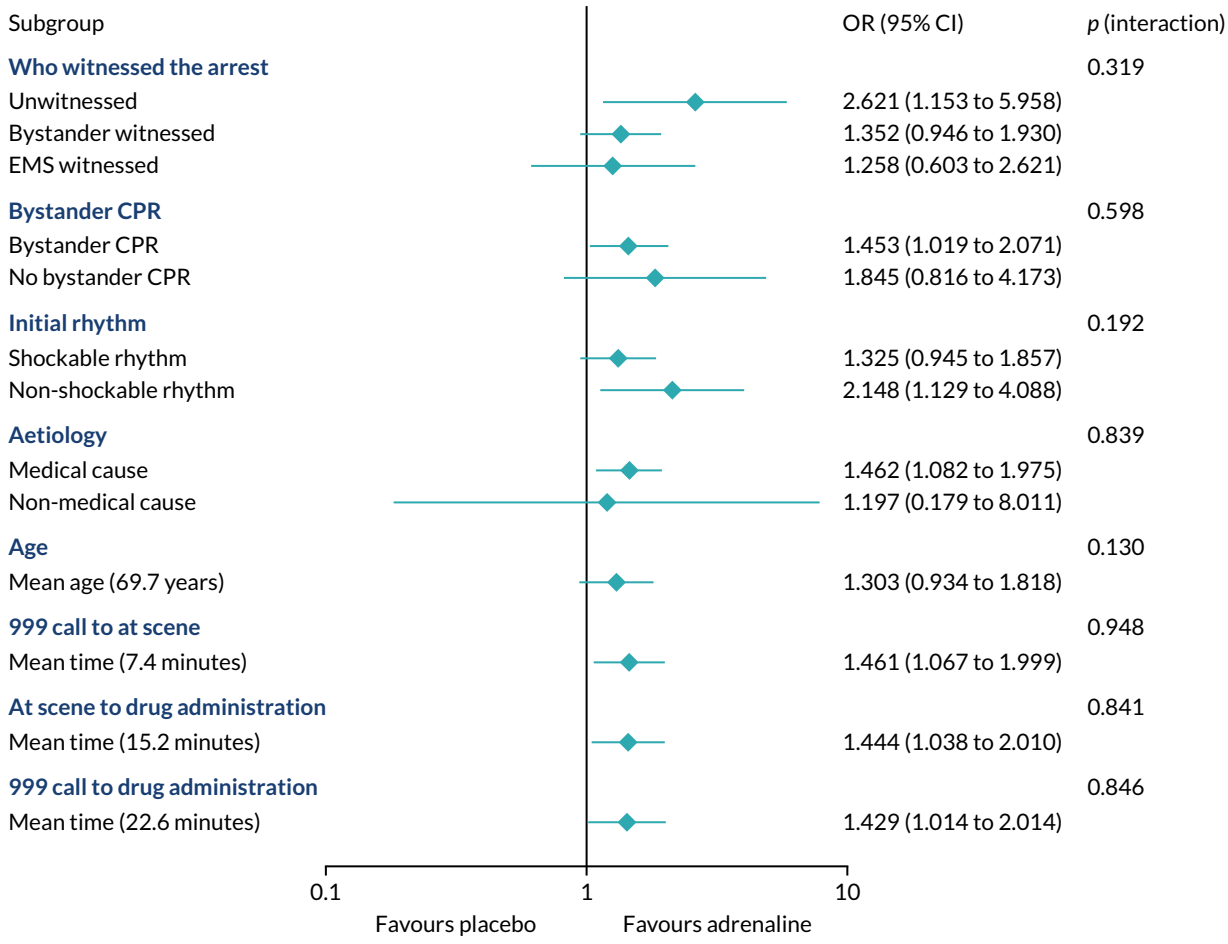

FIGURE 19 Adjusted subgroup analysis.

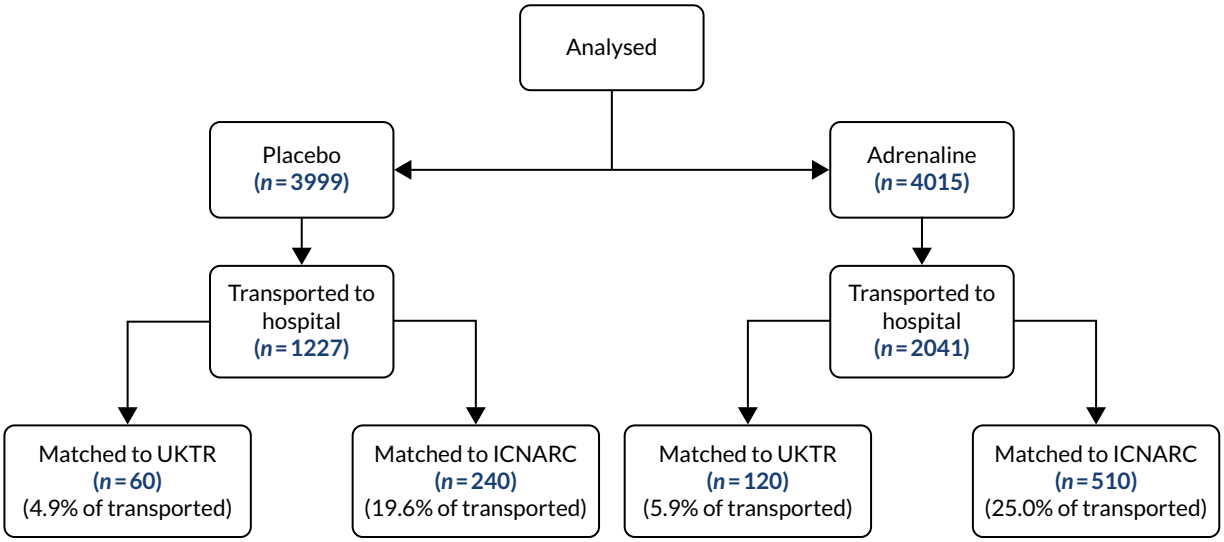

FIGURE 20 Data linkage to UKTR and ICNARC.

TABLE 12 Sensitivity analysis of short- to medium-term survival and mRS outcomes

Scenario	Trial arm, *n* (%)		Difference (95% CI) (%)	Unadjusted OR (95% CI)
	Adrenaline (*N* = 4015)	Placebo (*N* = 3999)		
30-day survival status				
A	133 (3.3)	98 (2.5)	0.9 (0.1 to 1.6)	1.36 (1.05 to 1.78)
B	130 (3.2)	94 (2.4)	0.9 (0.2 to 1.6)	1.39 (1.06 to 1.82)
C	130 (3.2)	98 (2.5)	0.8 (0.1 to 1.5)	1.33 (1.02 to 1.74)
D	133 (3.3)	94 (2.4)	1.0 (0.2 to 1.7)	1.42 (1.09 to 1.86)
E	–	–	–	1.38 (1.06 to 1.81)
Survived to hospital discharge				
A	134 (3.3)	95 (2.4)	1.0 (0.2 to 1.7)	1.42 (1.09 to 1.85)
B	128 (3.2)	91 (2.3)	0.9 (0.2 to 1.6)	1.41 (1.08 to 1.86)
C	128 (3.2)	95 (2.4)	0.8 (0.1 to 1.5)	1.35 (1.03 to 1.77)
D	134 (3.3)	91 (2.3)	1.1 (0.3 to 1.8)	1.48 (1.13 to 1.94)
E	–	–	–	1.41 (1.07 to 1.85)
90-day survival status				
A	127 (3.2)	94 (2.4)	0.8 (0.1 to 1.5)	1.36 (1.04 to 1.78)
B	121 (3.0)	86 (2.2)	0.9 (0.2 to 1.6)	1.41 (1.07 to 1.87)
C	121 (3.0)	94 (2.4)	0.7 (–0.0 to 1.4)	1.29 (0.98 to 1.70)
D	127 (3.2)	86 (2.2)	1.0 (0.3 to 1.7)	1.49 (1.13 to 1.96)
E	–	–	–	1.41 (1.07 to 1.87)
180-day survival status				
A	126 (3.1)	93 (2.3)	0.8 (0.1 to 1.5)	1.36 (1.04 to 1.79)
B	117 (2.9)	85 (2.1)	0.8 (0.1 to 1.5)	1.38 (1.04 to 1.83)
C	117 (2.9)	93 (2.3)	0.6 (–0.1 to 1.3)	1.26 (0.96 to 1.66)
D	126 (3.1)	85 (2.1)	1.0 (0.3 to 1.7)	1.49 (1.13 to 1.97)
E	–	–	–	1.38 (1.04 to 1.83)
Survival with good neurological outcome at discharge (mRS score of ≤ 3)				
A	95 (2.4)	79 (2.0)	0.4 (–0.2 to 1.0)	1.20 (0.89 to 1.63)
B	87 (2.2)	74 (1.9)	0.3 (–0.3 to 0.9)	1.17 (0.86 to 1.61)
C	87 (2.2)	79 (2.0)	0.2 (–0.4 to 0.8)	1.10 (0.81 to 1.50)
D	95 (2.4)	74 (1.9)	0.5 (–0.1 to 1.1)	1.29 (0.95 to 1.75)
E	–	–	–	1.18 (0.86 to 1.61)
Survival with good neurological outcome at 3 months (mRS score of ≤ 3)				
A	111 (2.8)	83 (2.1)	0.7 (0.0 to 1.4)	1.34 (1.01 to 1.79)
B	82 (2.0)	63 (1.6)	0.5 (–0.1 to 1.1)	1.30 (0.94 to 1.81)
C	82 (2.0)	83 (2.1)	–0.0 (–0.7 to 0.6)	0.98 (0.72 to 1.34)
D	111 (2.8)	63 (1.6)	1.2 (0.6 to 1.8)	1.78 (1.30 to 2.43)
E	–	–	–	1.30 (0.93 to 1.81)

continued

TABLE 12 Sensitivity analysis of short- to medium-term survival and mRS outcomes (*continued*)

Scenario	Trial arm, *n* (%)		Difference (95% CI) (%)	Unadjusted OR (95% CI)
	Adrenaline (*N* = 4015)	Placebo (*N* = 3999)		
Survival with good neurological outcome at 6 months (mRS score of ≤ 3)				
A	103 (2.6)	84 (2.1)	0.5 (–0.2 to 1.1)	1.23 (0.92 to 1.64)
B	78 (2.0)	58 (1.5)	0.5 (–0.1 to 1.1)	1.35 (0.96 to 1.90)
C	78 (2.0)	84 (2.1)	–0.1 (–0.8 to 0.5)	0.92 (0.68 to 1.26)
D	103 (2.6)	58 (1.5)	1.1 (0.5 to 1.7)	1.79 (1.29 to 2.48)
E	–	–	–	1.36 (0.97 to 1.92)

A, Best-case scenario in both arms; B, worst-case scenario in both arms; C, best-case scenario in the placebo arm and worst-case scenario in the adrenaline arm; D, best-case scenario in the adrenaline arm and worst-case scenario in the placebo arm; E, multiple imputation assuming missing at random.

TABLE 13 Frequency of protocol deviations and violations

	Frequency (*n*)
Type of deviation	
Expired trial drug pack used (used within 12-month shelf life)	6
Two trial packs opened for one patient (when all 10 doses from the first pack had been administered)	4
Open-label adrenaline given after 10 doses of the IMP	19
No active notification of patient enrolment to research team (no effect on follow-up of patient)	359
One pack used for two patients	8
Other	32
Total	428
Type of violation	
Expired trial drug pack used (used after end of 12-month shelf life)	3
Paramedic enrolled patient without completing trial training	19
Two trial packs opened for one patient (when < 10 doses had been administered from the first pack)	10
Ineligible patient enrolled (known to be ineligible at the point of randomisation)	8
Open-label adrenaline given after < 10 doses of the IMP	40
Other (IMP administered post ROSC; trained paramedic did not travel to A&E with untrained crew; patient's relatives contacted after they had declined consent for follow-up)	3
Total	83

A&E, accident and emergency.

Investigational Medicinal Product management

During scheduled reconciliation of the IMP (batches 6.2 and 6.3), the number of unaccounted packs in one ambulance service reached 4.4%. An investigation was instigated and the results were reviewed by the TMG. It was concluded that the risk to trial subjects, the public and to the scientific value of the trial was low. However, it was discussed with the MHRA and classified as a serious breach due to non-compliances associated with IMP management. A corrective and preventative actions plan was put in place, which included several communications to paramedic crews, thorough tracking of the drug pack journey for unaccounted packs and more regular drug audits. The rate of unaccounted-for packs reduced to 3.3% for future batch reconciliation and 2.7% overall. The serious breach was considered closed by the MHRA on 27 July 2017.

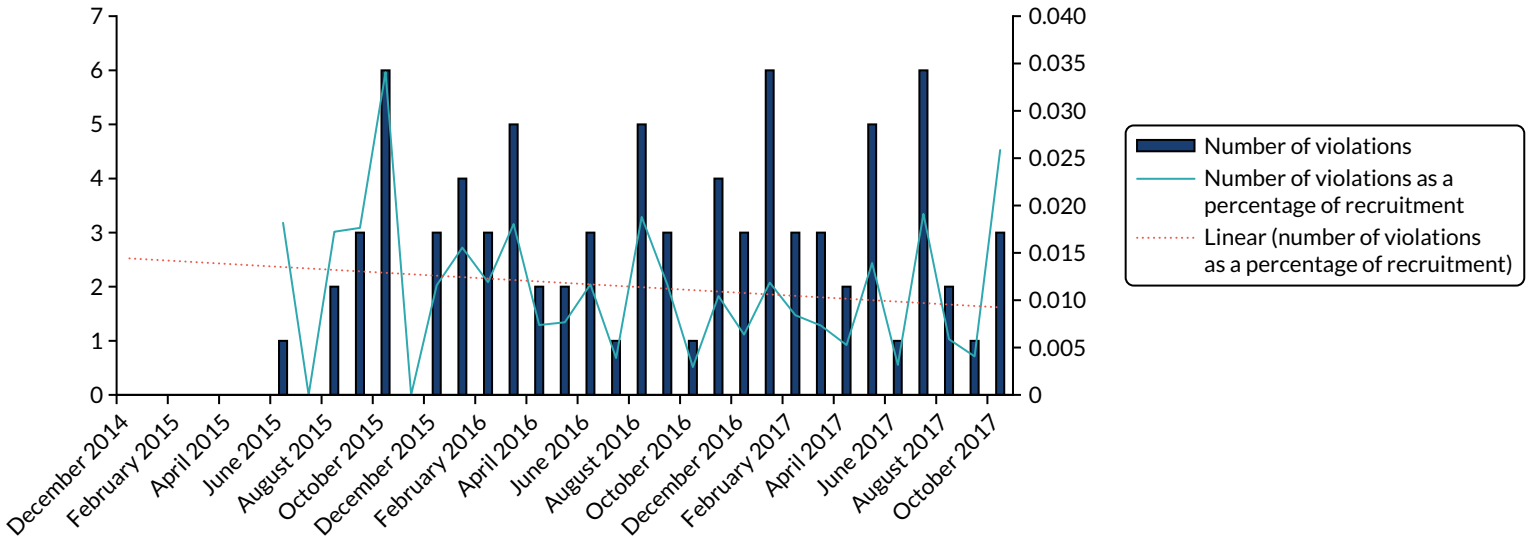

FIGURE 21 Frequency of protocol violations over time.

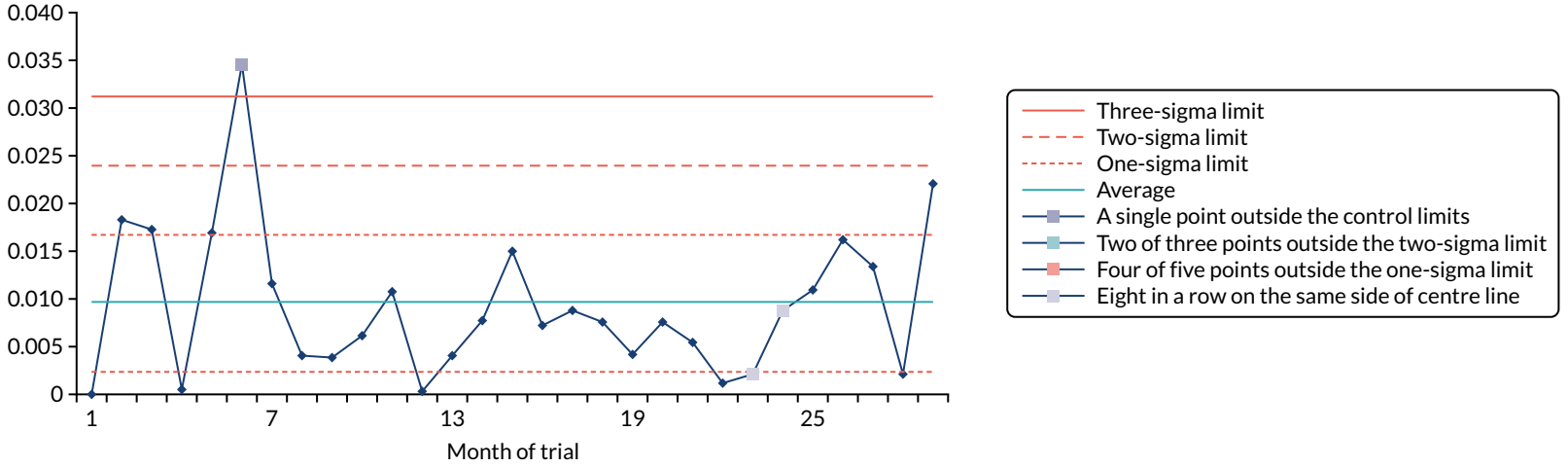

FIGURE 22 Statistical process control chart of the frequency of protocol violations over time as a percentage of recruitment.

Enrolment error, trial number 7398

A patient was enrolled who met one of the trial exclusion criteria. The HM Coroner inquest found that the error did not contribute to the patient's death. A root-cause analysis found that the paramedic did not adequately check the contents of the syringe before administering it; therefore, incorrect medicines were selected and given. This was reported to the MHRA as a potential serious breach, and was considered closed on 28 August 2018.

Corrective and preventative actions

The following preventative measures were in place prior to this incident occurring:

- Face-to-face trial refresher training had been provided to clinicians on an ongoing basis.
- Paramedics were provided with aide memoires detailing inclusion and exclusion criteria.
- Eligibility criteria stickers had been added to all IMP packs to act as a reminder.
- A question-and-answer exercise was undertaken at South Central Ambulance Service giving examples of non-compliances and checking that teams were aware of the correct course of action.

The following additional actions were put in place following the incident:

- The enrolling paramedic was prevented from enrolling further patients in the trial until retraining had taken place.
- A communication was sent on two separate occasions to all paramedics in the ambulance service to act as a reminder of eligibility criteria.
- A message was sent to all ambulance service dashboards reminding clinicians to check patient eligibility before administering the PARAMEDIC2 trial IMP.
- Refresher training slides were updated to emphasise eligibility criteria.

Assessment of impact of protocol non-compliances

It is the assessment of the TMG that the trial complied with GCP and that the deviations, violations and serious breaches did not have any material impact on the trial findings.

Chapter 4 Economic evaluation

Overview

A prospective within-trial economic evaluation was conducted to estimate the cost-effectiveness of adrenaline, compared with placebo, for OHCA. Costs are expressed in Great British pounds (2017 price year) and health outcomes are expressed in terms of QALYs, 6-month overall survival and 6-month survival with good neurological function (mRS score of ≤ 3). The base-case analysis used intention-to-treat data covering the 6-month period from randomisation and was conducted from the perspective of the UK NHS and PSS.[132]

A decision-analytic model was used to extrapolate outcomes beyond the trial follow-up and to assess the cost-effectiveness of adrenaline over a lifetime time horizon. Costs and outcomes were discounted to present values at 3.5% per annum only when the time horizon of the analyses was > 1 year (i.e. the lifetime decision-analytic model). Sensitivity analyses explored the probable impact of alternative data inputs (e.g. as a result of adopting a broader societal perspective) and assumptions on cost-effectiveness outcomes. Subgroup analyses were conducted to estimate heterogeneity in cost-effectiveness outcomes. Findings are reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.[133]

Measurement and valuation of resource use

Economic costs were calculated using estimates of resource inputs associated with pre-hospital emergency response, including treatment costs, and using estimates of broader utilisation of hospital- and community-based health and social care services.

Initial emergency response

Resource inputs associated with the initial pre-hospital emergency response were extracted from the trial CRFs completed by research paramedics. These data included the number of emergency response staff/ambulance crew and vehicles in attendance, the duration of the emergency response and the cumulative adrenaline doses administered. Emergency response duration was defined as (1) the interval between the at-scene time (i.e. the time at which the emergency response team arrived at scene) and the left-scene time (or the time at which CPR was stopped if the left-scene time was not recorded) if the cardiac arrest occurred at home and the patient was pronounced dead at scene, or (2) the interval between at-scene time and arrival-at-hospital time if the patient survived and was taken to hospital.

It was assumed that one vehicle transported the patient to hospital if multiple vehicles were in attendance, with the remaining vehicles standing down and available for the next assignment. Consequently, a 1-hour stand-down time was added to the emergency response time for each patient to account for ambulance crew stand-down and restock time following discussions with the trial paramedics about duration of these activities under current UK clinical practice. Sensitivity analyses (see *Table 14*, sensitivity analyses 11 and 13) explored the impact of excluding the cost of emergency response crew stand-down and restock time on cost-effectiveness outcomes.

Initial emergency response data were generally collected for trial participants up to the point of death or hospital admission. This meant that trial data were not available to estimate some resource inputs for patients who died at scene. In particular, the trial CRFs did not record post-death ambulance crew activity, such as whether or not the deceased person was transported to a mortuary. Thus, it was assumed that patients pronounced dead at the scene of the cardiac arrest would be left at the scene

if the location of the cardiac arrest was the patient's home, and would be transported by emergency ambulance to the nearest hospital or public mortuary if the location of the cardiac arrest was a public place. Google Maps (Google Inc., Mountain View, CA, USA) [called from within R (The R Foundation for Statistical Computing, Vienna, Austria) via packages 'gmapsdistance' and 'googleway'] was then used to estimate ambulance travel time to the nearest hospital mortuary for the subgroup of patients whose arrest occurred in a public place. Sensitivity analyses explored the impact of variations in this assumption on the base-case cost-effectiveness results (see *Table 14*, sensitivity analyses 12 and 13).

Hospital- and community-based health and social care service use

Data on the use of hospital- and community-based health and social care services covering the 6-month period from randomisation were collected for trial participants by three principal means:

1. Trial CRFs completed by research paramedics provided details of the initial hospitalisation episode, including ED assessment and treatment and inpatient length of stay in the ICU and cardiac and general adult wards.
2. Hospital Episode Statistics[134] were requested for trial participants, covering the period from each participant's cardiac arrest event to 31 March 2018. This provided a complete profile of resource use associated with all hospital episodes for all participants over the trial time horizon, including ED attendances, outpatient attendances, day-case admissions and critical care and other inpatient admissions covering procedures undertaken and lengths of stay. When HES data were not available, data collected using the trial CRFs and patient self-reports of hospital-based service use were used instead.
3. Economic questionnaires completed by trial participants or their proxies at the 3- and 6-month post-randomisation assessment points provided details of hospital re-admissions and use of hospital outpatient services, community health and social care services, prescribed medications, NHS supplies, child-care costs, time off work and out-of-pocket medical expenses.

Valuation of hospital resource use collected through trial case report forms

Hospital resource inputs were estimated for trial participants using the trial CRFs and valued by attaching unit costs drawn largely from secondary sources. Hospital-based services included inpatient admissions, outpatient visits and diagnostic tests and scans. Unit costs for these services were obtained primarily from the 2016/17 NHS reference costs main schedules,[135] and acted as an alternative source of hospital cost values to the HES-generated data. Average daily unit costs were calculated for hospital-based services using a costing methodology previously described in a HTA report that informed an economic evaluation of a mechanical versus manual CPR for OHCA.[136] The costing method involves assigning identifying Healthcare Resource Group (HRG) codes for clinical care most likely to be received following OHCA and calculating a per diem cost weighted by the level of activity.

Valuation of Hospital Episode Statistics data

The *HRG4+ 2016/17 Reference Costs Grouper*[137] was used to generate HRG codes for each record of admitted care and critical care episode, ED attendance, and outpatient visit extracted from HES for each trial participant. Records were matched to grouper costs in the 2016/17 NHS Reference Costs main schedules[135] based on the HRG and combination variables describing the level of resource use associated with each episode of care. ED and outpatient attendances were matched to averaged reference costs based on the HRG code only. Admitted care episodes were matched at the full consultant episode level based on the HRG, patient classification (admitted vs. day case), type of admission (elective vs. non-elective) and length of stay (short stay vs. long stay). Inpatient length of stay was defined as short stay if the episode duration was 1 day and was described as long stay for episodes lasting ≥ 2 days, in line with national reference cost calculations (see pages 47 and 48 of the *National Cost Collection guidance 2018*[138]).

Unbundled HRGs associated with high-cost drugs, devices and investigations and excess bed-days were automatically generated by the Grouper software for each admitted care record. Reference costs were attached to unbundled HRGs and excess bed-day costs generated by multiplying the duration of excess bed-days by respective excess bed-day unit costs in the 2016/17 reference cost schedules.[135] Costs were summed across full consultant episodes within spells to generate total costs per admitted care spell covering the total time period between admission and hospital discharge. Critical care records were matched to reference costs based on the critical care HRG, and critical care unit function code describing type of critical care activity. Non-specific general adult critical care patients and the maximum number of organ systems supported at any one time during the critical care period predominate in the algorithms were used to cost critical care episodes.[139]

Resource use and economic costs extracted from participant-completed questionnaires

Economic questionnaires completed by trial participants or their proxies at the 3- and 6-month post-randomisation assessment points provided resource use data that complemented the resource use data extracted from the trial CRFs and HES data sets. Details of hospital re-admissions, by type and duration of hospital admission and hospital outpatient service, by type and volume, were extracted from the economic questionnaires and valued using 2016/17 NHS reference costs main schedules.[135]

Primary and community health and social care services included face-to-face or telephone contacts and/or home visits by a general practice doctor, practice nurse, community physiotherapist or other community health or social care professionals. Consultation costs were derived from the Personal Social Services Research Unit's *Unit Costs of Health and Social Care 2017*.[140] The cost of prescribed medication was obtained primarily from the prescription cost analysis 2017 database[141] and electronic searches of the *British National Formulary* (BNF) 2017 edition.[142] Typical dosages and durations of treatment reported in the BNF for each medication were used in calculating quantities of individual preparations if the daily dose and/or duration of a course of medication was not reported in the trial documentation.

The quantities of over-the-counter medicines were rounded to the nearest pack and unit costs were obtained from online sources. Costs of aids and supplies (e.g. walking aids, heart monitors) were either provided by the trial participants themselves (if self-purchased) or derived from the NHS supply chain catalogue for aids and supplies provided by health providers during the trial follow-up period. Unit costs for health-care resource inputs were inflated/deflated to 2016/17 prices when necessary using the NHS Hospital and Community Health Services Pay and Prices Index, and the Consumer Prices Index.[140]

The economic questionnaires completed by trial participants or their proxies at the 3- and 6-month post-randomisation assessment points also provided details of broader societal (non-NHS/PSS) resource input and costs, such as out-of-pocket medical expenses (e.g. privately purchased medication, travel costs as a result of hospital and medical appointments), child-care costs, income lost, housework help and laundry services costs. Out-of-pocket medical expenditure (e.g. medication purchased by patients themselves and travel costs) were either provided in monetary terms or valued by attaching unit costs to resource inputs provided. Non-health-care costs such as child-care costs and lost income were generally provided by participants and/or their proxies in monetary terms; therefore, no requirement to value these outcomes was necessary.

Estimation of costs for the total 1-year period after randomisation

Hospital Episode Statistics[134] were requested for trial participants covering the period from the cardiac arrest event to 31 March 2018. This meant that patients followed up after this date had incomplete HES records covering the 1-year period after the cardiac arrest event. The following methodology was

used to calculate 1-year hospital costs estimates for all inpatients, including those with < 1 year of complete HES data:

- Hospital Episode Statistics data were available for 1833 (45.7%) participants in the adrenaline group and 1094 (27.4%) participants in the placebo group. Of these, complete records of hospital resource use up to 1 year were available for 1802 (98.3%) of the 1833 in the adrenaline group and 1068 (97.6%) of the 1094 in the placebo group. These data were used to estimate costs of hospital care (initial hospitalisation episode, re-admissions and use of non-admitted hospital care services such as day-case admissions, ED attendances and outpatient attendances) covering the period between the cardiac arrest event to 1 year post event. The remaining 31 (1.7%) patients in the adrenaline group and 26 (2.4%) in the placebo group had HES-based records of hospital resource use for < 1 year. The 1-year costs of hospital resource use for these patients were treated as missing data.
- Of the remaining 2182 (54.3%) trial participants in the adrenaline group and 2905 (72.6%) trial participants in the placebo group who did not have HES data, 1984 (90.9%) in the adrenaline group and 2778 (95.6%) in the placebo group died at the scene of the cardiac arrest or were not taken to hospital. We assigned zero hospitalisation costs to these patients. The remaining 198 (8.1%) and 127 (4.4%) participants in the adrenaline and placebo groups, respectively, who were taken to hospital but had no HES records were either treated as missing data (if they declined consent to continued participation) or assigned 1-year hospitalisation costs based on the CRFs and data collected through the economic questionnaires completed by trial participants or their proxies.
- The cost of hospital resource use covering the 0–6 months post-randomisation period was estimated based on resource use extracted from the CRF and economic questionnaire data. The costs of hospital re-admissions and non-admitted care services in the 6- to 12-month window were estimated by extrapolating costs incurred in the 3- to 6-month period to 6–12 months. This essentially multiplied the 3- to 6-month costs by three for the calculation of 1-year hospital costs.
- Finally, 1-year costs associated with the use of non-hospital-based health and social care services and societal costs were estimated by extrapolating costs incurred at 3–6 months post randomisation (derived from participant-completed questionnaires) to 6–12 months post randomisation for all trial participants.

Measurement of outcomes

Health-related quality of life and survival

Health-related quality of life was assessed using generic instruments (i.e. the EQ-5D-5L and SF-12 version 2) completed at 3 and 6 months post randomisation and the mRS instrument completed at hospital discharge and at 3 and 6 months post randomisation. Responses to the EQ-5D-5L descriptive system were converted into health utility (or preference-based health-related quality-of-life) values, based on the UK EuroQol-5 Dimensions, three-level version (EQ-5D-3L), tariff[143] using the van Hout *et al.*[144] interim cross-walk algorithm, in line with current NICE recommendations.[145] The mRS scores were converted into health utility (or preference-based health-related quality-of-life) values, based on the UK EQ-5D-3L tariff,[143] using a published mapping function developed by Rivero-Arias *et al.*[146] The SF-12 scores were converted into health utility values using the Short Form questionnaire-6 Dimensions (SF-6D) utility tariff for the UK published by Brazier *et al.*[147] Survival outcomes following cardiac arrest were also collected to 12 months post cardiac arrest for trial participants.

Quality-adjusted life-years

Quality-adjusted life-year profiles were generated for each trial participant using area-under-the-curve methods, assuming a baseline health utility value of zero and linear interpolation between utility measurements, taking into account survival over the 6-month time horizon of interest (base case). In the base-case analysis, we combined utility values from the mRS scores at hospital discharge and utility values derived from the EQ-5D-5L at 3 and 6 months to calculate QALY profiles over 6 months. We used mRS-derived health utilities in place of EQ-5D-5L values if the latter were missing at the 3- or 6-month

post-randomisation assessment points.[146] Health utility values generated from the mRS were available at hospital discharge and at all assessment points over the 6-month base-case time horizon. Thus, the impact of combined EQ-5D-5L-/mRS-generated QALYs on the base-case cost-effectiveness results was assessed in a sensitivity analysis that used QALYs generated solely from the mRS scores. Patients who died were assigned a utility value of zero onwards from time of death for the calculation of QALYs.

We did not assess health-related quality of life at baseline, as the clinical context precluded collecting any patient-reported outcome data around the time of randomisation: patients were either unconscious or too critically ill to complete questionnaires.[148] Alternative assumptions around health-related quality of life at baseline explored the impact on the cost-effectiveness of adrenaline of setting the baseline utility value to zero. In the first of these, the baseline utility value in the adrenaline and placebo groups was set to −0.402, reflecting UK population preferences for an unconscious health state within the EQ-5D-3L A1 tariff set.[149]

We also calculated QALY profiles over 12 months, under the assumption that patients' health-related quality of life at 12 months was the same as their health-related quality of life at 6 months, if they had survived, and we used this information to inform a sensitivity analysis exploring longer-term cost-effectiveness.

Statistical analysis of economic data

Summary of resource use and costs

Patient-level costs were generated for each resource variable by multiplying the quantity reported by the respective unit cost, weighted by length of stay or duration of contact when appropriate. Summary statistics (means, standard errors and completion rates) were generated for the whole trial population and for those surviving to hospital discharge by treatment allocation and assessment point. Between-group differences in mean resource use and mean costs at each assessment point were compared using the two-sample *t*-test. Statistical significance was assessed at the 5% significance level. A non-parametric bootstrap routine was implemented, generating 1000 replications of the data. Estimates of standard errors surrounding mean resource use (or cost) estimates and 95% CIs surrounding between-group differences in mean resource use (or costs) were obtained from the bootstrapped samples.

Summary of health-related quality-of-life data

Responses to each health dimension of the EQ-5D-5L and SF-12 are presented by level of function. Comparisons of responses were conducted on the basis of optimal level of function (e.g. 'no problem' on the EQ-5D-5L) versus suboptimal level of function (indicating any functional impairment). Between-group differences in optimal versus suboptimal level of function for each health dimension were compared for each outcome measure using chi-squared (χ^2) tests at each assessment point for each health-related quality-of-life instrument. Summary statistics (means, standard errors and completeness rates) for health utilities were generated for the whole trial population and for survivors to hospital discharge by treatment allocation, assessment point and health-related quality-of-life instrument. Estimates of between-group difference in mean health utility values and 95% bootstrapped CIs surrounding mean group differences were generated based on 1000 bootstrapped resamples of the data.

Missing data

In addition to trial-specific protocols and procedures to minimise missing data, a strategy was employed prior to commencement of recruitment to identify and collect resource use and health outcomes data from multiple sources, with the specific aim of reducing the level of missingness for the economic outcomes of interest. Participants were assumed to incur no health-care costs beyond the initial emergency response costs if cardiac arrest occurred at home and the patient was declared deceased at the scene of arrest. Costs associated with use of hospital-based services were generated primarily from HES data; information obtained through trial-specific procedures (trial CRFs and participant questionnaires) was used when HES data were not available.

Health-related quality of life was assessed using multiple instruments, including the mRS completed at hospital discharge and the mRS, EQ-5D-5L and SF-12 completed by trial participants at 3 and 6 months post randomisation. Survival information was collected through trial-specific procedures and Office for National Statistics data. This process of using multiple data sources to systematically fill in missing data provided a more complete profile of the main economic outcomes of interest, compared with relying on a single data source.

Nevertheless, multiple imputation by chained equations (MICE), implemented through the R package MICE,[150] was used to predict values for any remaining missing items, assuming data were missing at random. Missing costs and health utility values were imputed at the level of resource category and health-related quality-of-life assessment, stratified by survival status at hospital discharge and treatment allocation in accordance with good-practice recommendations outlined in Faria *et al.*[151] Imputation was achieved using predictive mean matching, which has the advantage of preserving non-linear relationships and correlations between variables within the data. Twenty imputed data sets were generated and used to inform the base-case and subsequent sensitivity and subgroup analyses. Parameter estimates were pooled across the 20 imputed data sets using Rubin's rules to account for between- and within-imputation components of variance terms associated with parameter estimates.

Base-case cost-effectiveness

The base-case cost-effectiveness analysis used the intention-to-treat data to estimate the cost–utility of adrenaline, compared with placebo, from the perspective of the UK NHS and PSS.[132] Economic costs and QALYs were calculated for each patient over a 6-month post-randomisation time horizon. Total costs were calculated by summing costs associated with the initial emergency response (including the cost of the intervention) and costs of broader hospital- and community-based health and social care services. QALYs were generated based on health utility data generated from the mRS score at hospital discharge and the EQ-5D-5L score at the 3- and 6-month assessments.

Two seemingly unrelated normal error regressions were fitted to imputed data using the systems fit implementation in R,[152] which accounts for the correlation between patient-level costs and QALYs. The regressions controlled for treatment allocation, age, sex, time to first dose administration, cause of cardiac arrest, whether or not the cardiac arrest was witnessed, bystander CPR and rhythm. The base-case analyses were replicated using the Stata® version 15 (StataCorp LP, College Station, TX, USA) MICE and seemingly unrelated regressions SUR REG functions.

The incremental cost-effectiveness ratio (ICER) was calculated for adrenaline, compared with placebo, by dividing the between-group difference in adjusted mean total costs by the between-group difference in adjusted mean QALYs. Cost-effectiveness was assessed by comparing the ICER to cost-effectiveness thresholds of between £15,000 and £30,000 per QALY gained, in line with NICE guidance[132] and the recent empirical threshold of £13,000 per QALY estimate suggested by Claxton *et al.*[153] Estimates were also generated assuming £50,000 and £100,000 values for the cost-effectiveness threshold for a QALY, reflecting potentially higher willingness-to-pay thresholds for a life-saving intervention. The incremental net (monetary) benefit of adrenaline compared with placebo was calculated for cost-effectiveness thresholds ranging from £15,000 to £200,000 per QALY gained. Net monetary benefit values reflect the opportunity cost of (or the benefits forgone from) adopting a new treatment when resources could be put to use elsewhere. A positive net monetary benefit suggests that, on average, adrenaline provides a net gain, compared with placebo, for the health service and can be considered cost-effective at the given cost-effectiveness threshold.

Uncertainty around the mean cost-effectiveness estimates was characterised through a Monte Carlo method.[154] This involved simulating 1000 replicates of the ICER from a joint distribution of the incremental costs and QALYs and plotting the simulated ICERs on the cost-effectiveness plane. A sensitivity analysis explored an alternative characterisation of uncertainty based on generating 1000 bootstrap replications of the ICER instead of the Monte Carlo method (see *Table 14*, sensitivity analysis 4). Cost-effectiveness

acceptability curves (CEACs) were also plotted to give graphical display of the probability that adrenaline is cost-effective across a wide range of cost-effectiveness thresholds. A sensitivity analysis explored the impact of embedding the imputation model within the non-parametric bootstrap to simulate 1000 replicates of the ICER to calculate the probability that adrenaline is cost-effective at the cost-effectiveness thresholds specified previously.

Analysis of secondary health economic outcomes

Secondary health economic outcomes were analysed using logistic regression models that were embedded in the bootstrap and imputation models. The regression models estimated adjusted overall survival and neurologically intact survival probabilities for adrenaline and placebo at 6 months post randomisation. This preserved the correlation between patient-level costs and effects and allowed us to express the cost-effectiveness of adrenaline as incremental costs per unit increase in the proportion of patients surviving to 6 months post cardiac arrest.

Sensitivity analyses

Table 14 summarises methods and assumptions underlying the base-case and the sensitivity analyses conducted to explore the impact of alternative modelling assumptions and methods on the cost-effectiveness of adrenaline.

TABLE 14 Prespecified and post hoc sensitivity analyses exploring the impact of various modelling assumptions on base-case cost-effectiveness

Sensitivity analysis	Base-case methods/assumptions	Changes implemented in sensitivity analyses
Prespecified		
1	Adjusted multiple imputation	Unadjusted multiple imputation
2	Adjusted multiple imputation	Adjusted complete-case analysis
3	Adjusted multiple imputation	Unadjusted complete-case analysis
4	Parameter estimates via seemingly unrelated linear regression	Parameter estimates via linear regression implemented within a boostrap
5	QALYs based on EQ-5D-5L/mRS data	QALYs based on mRS data only
6	QALYs derived assuming baseline utility of 0 (equivalent to dead)	QALYs derived assuming baseline utility of −0.042 (equivalent to unconscious health state)
7	QALYs based on EQ-5D-5L and mRS data, NHS/PSS costs	QALYs based on EQ-5D-5L and mRS data, 6 months' societal costs
8	6-month time horizon (QALYs based on EQ-5D-5L and mRS data, NHS/PSS costs)	12-month time horizon (QALYs based on EQ-5D-5L and mRS data, NHS/PSS costs)
9	QALYs based on EQ-5D-5L and mRS data, 6-month time horizon	12-month time horizon (QALYs based on mRS data, NHS/PSS costs)
10	QALYs based on EQ-5D-5L and mRS data, 6-month time horizon	12-month time horizon (QALYs based on EQ-5D-5L and mRS data, societal costs)
Post hoc analyses		
11	1 hour added to emergency response cost calculations to account for stand-down and restock time	Excluded stand-down and restock time in emergency response cost calculations
12	Accounts for cost of transporting deceased patients to nearest hospital or local authority mortuary if patient died at scene of cardiac arrest and in a public place	Excluded estimated cost of transporting deceased patients to nearest hospital mortuary if patient died at scene of cardiac arrest and in a public place
13	Accounts for stand-down/restock time and transportation costs to nearest mortuary if patients died in a public place in emergency response cost calculations	Excluded stand-down/restock time and cost of transporting patients to nearest mortuary in emergency response cost calculations

Subgroup analysis

Prespecified subgroup analyses were also conducted based on specifications in the PaRAMeDIC trial[81] statistical analysis plan to explore whether or not there are subgroups of patients for whom adrenaline is likely to be cost-effective. In addition, one post hoc subgroup explored the treatment dose–response relationship and estimated the dose at which adrenaline is likely to be most cost-effective. Our subgroup analyses were as follows:

- Cardiac arrest witnessed by paramedic versus cardiac arrest witnessed by bystander versus cardiac arrest not witnessed.
- Bystander CPR versus no bystander CPR for bystander-witnessed and not-witnessed OHCAs.
- Type of initial rhythm: shockable (VT/VF) versus non-shockable (PEA/asystole).
- Aetiology of cardiac arrest (medical vs. non-medical).
- Age (≤ 60 years vs. > 60 years).
- Time interval from 999 call to EMS arrival (≤ 10 minutes vs. > 10 minutes) among those with a witnessed arrest.
- Time interval from EMS arrival to administration of trial drug (≤ 10 minutes vs. > 10 minutes) among those with a witnessed arrest.
- Time interval from 999 call to administration of trial drug (≤ 10 minutes vs. > 10 minutes) among those with a witnessed arrest.
- The time to emergency treatment variables were categorised based on previous studies reporting that administration of adrenaline within 10 minutes following cardiac arrest is associated with neurologically improved survival outcomes.[155]

Extrapolating beyond trial follow-up

A simple Markov state-transition model was built in R using the package heemod[156] to extrapolate the within-trial results over the lifetimes of cardiac arrest survivors. The model as shown in *Figure 23* comprises four health states (OHCA state, post-OHCA survival with good neurological function, post-OHCA survival with poor/impaired neurological function and death). The cycle length is 1 year and all individuals start in the OHCA state at the incidence of cardiac arrest event. Possible transitions

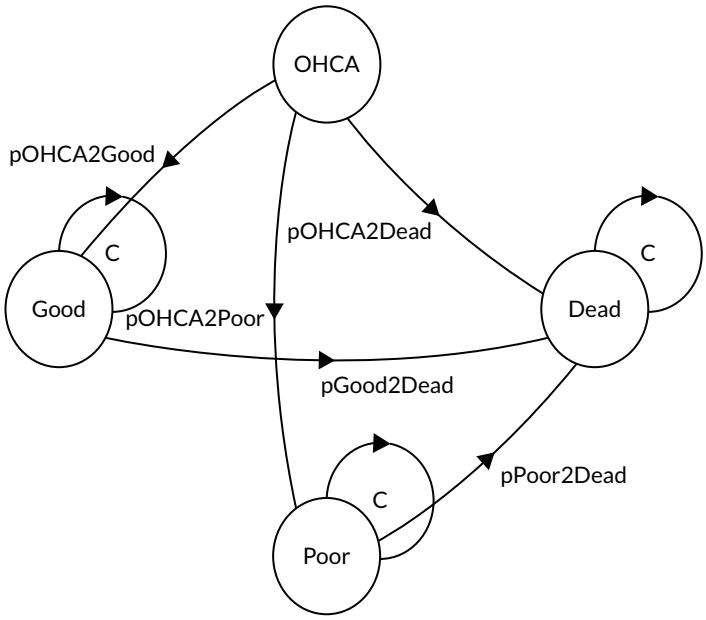

FIGURE 23 Model to extrapolate cost-effectiveness beyond the PARAMEDIC2 trial follow-up. C, complement (probability of remaining in good or poor neurological functional states); good, good neurological function; poor, poor neurological function; pGood2Dead, annual probability of death among survivors with good neurological function; pPoor2Dead, annual probability of death among survivors with poor neurological function; pOHCA2Dead, probability of death within first year post cardiac arrest/from randomisation; pOHCA2Good, probability of surviving to 1 year with good neurological function; pOHCA2Poor, probability of surviving to 1 year with poor neurological function.

from this state represent 1-year survival with good or poor neurological function and death. This implies that the OHCA state captures all the economic costs and benefits in the first year after randomisation and so corresponds to the within-trial cost-effectiveness analysis with a 1-year time horizon. In the PARAMEDIC2 trial, neurological function was assessed at hospital discharge and at 3 and 6 months post randomisation. This information was used to categorise post-OHCA survival as good if the score of the mRS assessment closest to the 1-year time point after the cardiac arrest was ≤ 3 and to categorise it as poor for scores of > 3. Probabilities governing these transitions were estimated separately for the adrenaline and placebo groups, based on these categorisations, and are summarised in *Table 15*.

TABLE 15 Extrapolating beyond trial follow-up; data inputs

Parameter	Mean (SE)	Distribution	Source
Cohort characteristics			
Mean age (years), 1-year post-cardiac arrest survivors	60		PARAMEDIC2 data
Percentage of males among 1-year post-cardiac arrest survivors	78	Beta	PARAMEDIC2 data
Probabilities			
1-year survival with good function (mRS score of ≤ 3), adrenaline	0.023 (0.0024)	Multinomial	PARAMEDIC2 data
1-year survival with good function (mRS score of ≤ 3), placebo	0.019 (0.0021)	Multinomial	PARAMEDIC2 data
1-year survival with poor function (mRS score of > 3), adrenaline	0.005 (0.0011)	Multinomial	PARAMEDIC2 data
1-year survival with poor function (mRS score of > 3), placebo	0.003 (0.0019)	Multinomial	PARAMEDIC2 data
3-month mortality given alive with good function at 9 months post arrest	0.029 (0.013)	Binomial	PARAMEDIC2 data
3-month mortality given alive with poor function at 9 months post arrest	0.061 (0.042)	Binomial	PARAMEDIC2 data
Annual mortality rate given survival to 1 year with good function	0.111 (0.0457)	Derived	0.111/UK mortality 2015[157]
Annual mortality rate given survival to 1 year with poor function	0.215 (0.1213)	Derived	0.215/UK mortality 2015[157]
Costs (£, 2017 prices)			
OHCA, adjusted mean costs, 1 year post randomisation, adrenaline	3741 (536)	Gamma	PARAMEDIC2 data
OHCA, adjusted mean costs, 1 year post randomisation, placebo	2330 (541)	Gamma	PARAMEDIC2 data
Good functional state	7907 (718)	Gamma	PARAMEDIC2 data
Poor functional state	24,457 (2275)	Gamma	PARAMEDIC2 data
Utilities (EQ-5D-5L)			
OHCA, adjusted mean utility, first year post randomisation, adrenaline	0.0038 (0.0051)	Beta	PARAMEDIC2 data
OHCA, adjusted mean utility, first year post randomisation, placebo	0.0061 (0.0051)	Beta	PARAMEDIC2 data
Good functional state	0.707 (0.019)	Beta	PARAMEDIC2 data
Poor functional state	0.0982 (0.0511)	Truncated normal	PARAMEDIC2 data

SE, standard error.

Possible transitions beyond the first year after the cardiac arrest event were restricted to movement from the good and poor functional states to death. The probabilities governing these movements were assumed to be independent of treatment allocation and were estimated from two sources. First, we estimated the conditional probability of surviving to 12 months, given that an individual had survived the first 9 months with good or poor function, and converted these estimates to 1-year probabilities using standard formulae.[158] Second, we obtained age- and sex-adjusted UK mortality statistics,[157] assuming a starting age of 60 years and 78% probability of being male, reflecting the average cohort characteristics of survivors at 1 year post randomisation. We used this information to extrapolate survival beyond the first year post cardiac arrest to a lifetime horizon by assigning individuals a probability of death equivalent to the larger of the two estimates.

We assumed that patients surviving beyond the first year after the cardiac arrest event either died or remained alive in the same functional state at each modelled cycle (functional status cannot improve or deteriorate after first year post cardiac arrest). The assumption that neurological function cannot improve or deteriorate after the first year post cardiac arrest was made because of a lack of robust data to estimate the between-state transitions, and is consistent with recent economic models evaluating the cost-effectiveness of intervention in cardiac arrest.[159]

Patients in the OHCA state were assigned cost and utility values obtained from the within-trial sensitivity analysis in which the time horizon was extended to 1 year. This covered the full spectrum of costs and QALYs incurred in the first year after the cardiac arrest event, adjusted for demographic and clinical characteristics. Costs associated with the good and poor functional states were estimated from resource use estimates covering the 3- to 6-month post-randomisation period collected for trial participants. Utility values associated with good and poor functional states were collected through the EQ-5D-5L reported by trial participants and stratified by functional status at the 6-month assessment point (see *Table 15*). Costs generated from resource use covering the 3- to 6-month period after randomisation were converted to 1-year costs assuming that the rate of resource use in this 3-month window is maintained over a period of 1 year. Costs and utilities were discounted at 3.5% per annum over the lifetime of cardiac arrest survivors.

Chapter 5 Results

Trial population

A total of 8014 participants were randomised in the PARAMEDIC2 trial: 4015 to the adrenaline group and 3999 to the placebo group (see *Figure 24*). Of these, 219 participants survived to hospital discharge: 128 in the adrenaline group and 91 in the placebo group.

In our estimation of economic outcomes of interest, we assigned a nominal value of zero to resource use, costs and health utility for patients who died at the scene of the cardiac arrest or prior to the collection of health-related quality-of-life data (in which case zeros were assigned to QALYs, but not resource use and costs). Thus, for all participants based on HES and CRF sources, approximately 98.9% and 99.2% of all health resource use data (including the zero service utilisation and utility assigned to deaths) were available at 3 months for the adrenaline and placebo groups, respectively; this dropped to 98.7% and 98.8%, respectively, by 6 months (see *Appendix 1*, *Tables 26* and *27*). Similarly, a complete QALY profile over the 6-month time horizon was estimated for 7939 of the 8014 (99.1%) trial participants, based on utility weights derived from the EQ-5D-5L and mRS assessments at hospital discharge and at 3 and 6 months post randomisation (see *Table 22*).

When looking at the completeness rates for survivors (see *Table 23*), approximately 72.7% and 71.4% of all health resource use data reported on the CRFs were complete at 3 months for the adrenaline and placebo groups, respectively; this declined to 63.3% and 51.6%, respectively, by 6 months (see *Appendix 1*, *Tables 30* and *31*). A complete QALY profile based on the EQ-5D-5L and mRS utility scores was available for 132 out of 219 (60.3%) survivors at 6 months post randomisation.

Overall, approximately 1% of QALY data and between 1% and 2% of costs (at the component level) were missing (and subsequently imputed) for the primary analysis.

Resource use and costs extracted from Hospital Episode Statistics

Figure 24 displays the flow chart of data sources used to inform estimates of resource use and costs. HES data were requested for 2023 (50.4%) of the 4015 patients in the adrenaline arm and for 1214 (30.4%) of the 3999 patients in the placebo arm. This represented data for trial participants who survived to hospital admission and who did not withdraw consent to participate in the trial. Of those requested, HES records covering the 6-month (1 year for some patients) period from the cardiac arrest event were provided by NHS Digital and PEDW for 1833 patients in the adrenaline arm and 1094 in the placebo arm, generating linkage rates of 90.6% and 90.1% for the adrenaline and placebo arms, respectively. This represented 45.7% of the 4015 patients randomised to adrenaline and 27.4% of the 3999 patients randomised to placebo. For the remaining 2182 (54.3%) patients in the adrenaline arm who did not have HES data provided, 2171 (99.5%) died prior to hospital admission (and therefore incurred no costs beyond the initial emergency response costs) and 11 (0.5%) had no linkage records or survived to decline consent to continued participation in the trial. For the placebo arm, 2905 (72.6%) of the 3999 patients did not have HES data provided: 2893 (99.6%) died before they could be admitted to hospital and 12 (0.4%) either declined consent or had no linked records for analysis. Summaries of hospital resource use (length of stay in a hospital inpatient ward and ICU admissions, day-case admissions, and ED and outpatient attendances), by trial arm and follow-up period, extracted from the HES records are presented in *Appendix 1*, *Table 26*. Summary statistics were generated based on the available HES records at each level of hospital resource use, and therefore excluded trial participants who were not admitted to hospital (e.g. those who died at home), those who declined

continued consent and those admitted to hospital but who had no record for a particular category or level of hospital resource use variable.

During the initial hospitalisation event among the 1833 (45.7%) and 1094 (27.4%) patients with HES data in the adrenaline and placebo arms, respectively (see *Appendix 1*, *Table 26*), there were no noticeable differences between the adrenaline and placebo arms in mean hospital length of stay (6.63 vs. 7.84 days, respectively; unadjusted mean difference −1.2 days, 95% bootstrapped CI −3.5 to 0.91 days) and ICU length of stay (5.75 vs. 6.29 days, respectively; mean difference −0.54 days, 95% CI −2.13 to 1.07 days). There were no noticeable differences between the adrenaline and placebo groups in length of stay in a general ward (18.55 vs. 16.69 days, respectively; mean difference 1.86 days, 95% CI −9.84 to 13.71 days) or an ICU (9.8 vs. 13.29 days, respectively; mean difference −3.49 days, 95% CI −12.96 to 6.31 days) for hospital re-admissions over the 6-month period after the cardiac arrest. Similarly, there were no differences between the adrenaline and placebo arms in ED attendances (1.05 vs. 1.04 visits, respectively; mean difference 0.01 visits, 95% CI −0.02 to 0.03 visits), day-case attendances (5.93 vs. 1.06 visits, respectively; mean difference 4.87 visits, 95% CI −0.12 to 15.8 visits) and outpatient attendances (5.12 vs. 6.07 visits, respectively; mean difference −0.95, 95% CI −2.58 to 0.68 visits).

Thirty-one (1.7%) of the 1833 trial participants with HES data in the adrenaline arm and 26 (2.4%) of the 1094 patients with HES data in the placebo arm who had their cardiac arrest event after 31 March 2017 were alive 1 year after arrest; therefore, these patients had partially incomplete 1-year records of hospital resource use based on the HES data. We assumed that hospital resource use data covering the 6- to 12-month period after the cardiac arrest event are missing for these patients because of incompleteness of follow-up. For the remaining 1802 (98.3%) of the 1833 patients in the adrenaline arm and 1068 (97.6%) of the 1094 in the placebo arm, complete records of hospital resource use were available for the 1-year period after the cardiac arrest event and are summarised in *Appendix 1*, *Table 26*. There were no noticeable differences between the adrenaline and placebo arms in hospital length of stay or ICU length of stay during hospital re-admissions in the 6- to 12-month period after the cardiac arrest event. Similarly, there were no differences between the two groups in ED attendance and day-case attendances, but the adrenaline arm had significantly more outpatient consultations, on average, than the placebo arm (7.45 vs. 4.3 visits, respectively; unadjusted mean difference 3.15 visits, 95% CI 0.31 to 6.74 visits).

Appendix 1, *Table 27*, presents hospital-related costs based on HES-only data for the 0- to 6-month and 0- to 12-month post-cardiac arrest periods by trial arm and resource category. As explained in *Chapter 4*, *Valuation of hospital resource use collected through trial case report forms*, these costs were derived by mapping HRG codes generated using the *HRG4+ 2016/17 Reference Costs Grouper*[137] to national reference costs.[135] Across all categories of hospital services, the mean total cost per patient estimated from the HES data was £5224 for the adrenaline arm and £4777 for the placebo arm, generating a mean cost difference of £448 (95% CI −£718 to £1483; $p = 0.412$) during the 0- to 6-month period following the cardiac arrest event.

Costs of hospital-based services covering the period of 0–12 months after the cardiac arrest event are also summarised in *Appendix 1*, *Table 27*. As explained previously, only participants with complete 1-year HES records are included in the calculation of these costs. The mean total cost of hospital resource use over 12 months was £4913 for the adrenaline arm and £4350 for the placebo arm, generating a mean 1-year cost-difference of £563 (95% CI −£660 to £1644; $p = 0.314$).

Summaries of the NHS and PSS resource use values by trial allocation, resource category and trial period for complete cases collected through trial CRFs and participant-completed questionnaires are presented in *Appendix 1*, *Table 28*, for all patients and in *Appendix 1*, *Table 30*, for survivors. The equivalent summaries for non-NHS and PSS resource use information are also presented in *Appendix 1*, *Table 29*, for all patients and in *Appendix 1*, *Table 31*, for survivors. Resource use values are presented

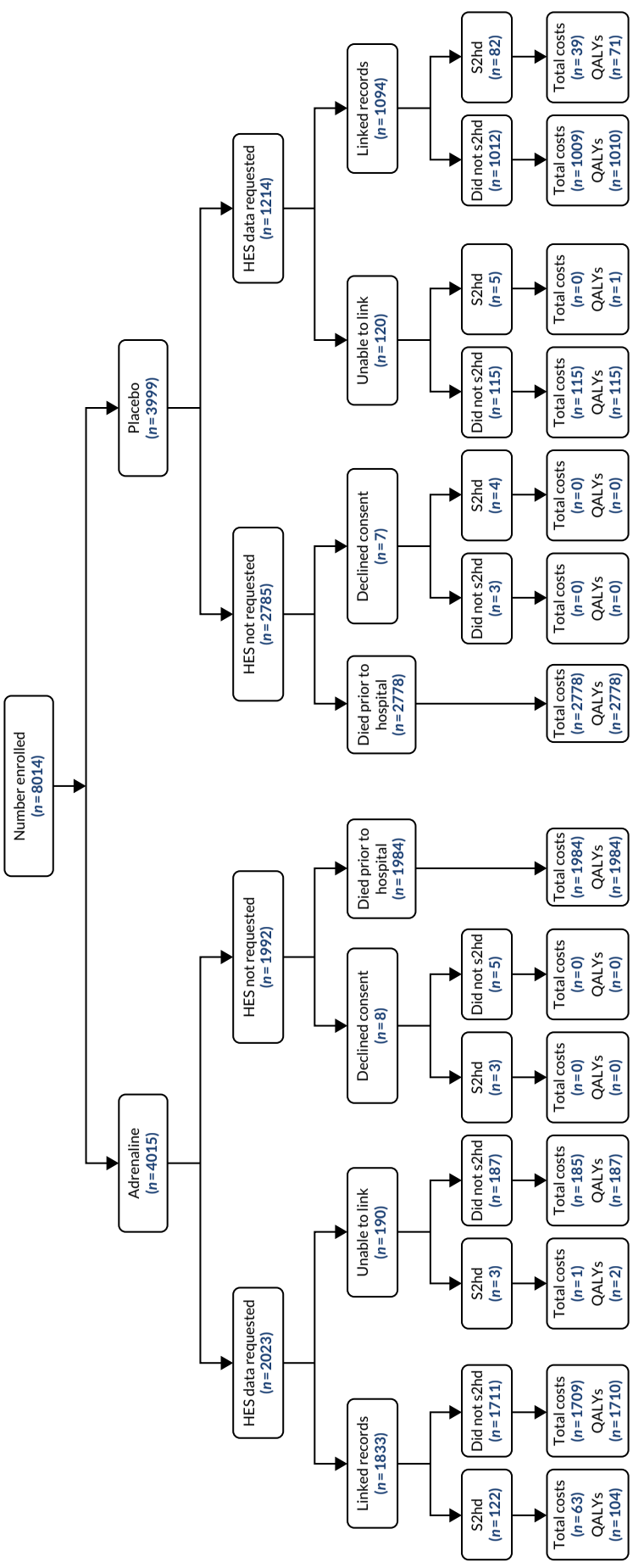

FIGURE 24 Flow chart of data sources used to inform estimation of resource use and costs. Resource use data were collected through trial CRFs. S2hd, survive(d) to hospital discharge.

for subcategories of resource use, including emergency response, intervention doses administered, hospital inpatient and outpatient care, primary health care (residential care, community health and social care), prescribed medications, and equipment and aids. Broader societal resource inputs and costs included privately purchased medications, travel costs, child care, income lost, help with housework and laundry service costs (see *Appendix 1*, *Tables 29* and *31*).

In terms of specific resource use values from an NHS and PSS perspective for adrenaline versus placebo for all participants at 3 months (see *Appendix 1*, *Table 28*), notable differences were observed for number of syringes given (mean difference for adrenaline vs. placebo −0.152 syringes, 95% bootstrapped CI −0.266 to −0.052 syringes), ED stays (mean difference 0.201 days, 95% CI 0.179 to 0.224 days), general ward stays (mean difference 0.296 days, 95% CI 0.078 to 0.536 days) and ICU stays (mean difference 0.438 days, 95% CI 0.298 to 0.592 days). When looking at the equivalent information for survivors to hospital discharge at 3 months (see *Appendix 1*, *Table 28*), there were no noticeable differences between the trial arms.

Between 3 and 6 months post cardiac arrest, for all participants (see *Appendix 1*, *Table 28*), evidence of noticeable differences in resource use from an NHS and PSS perspective between adrenaline and placebo was observed for district nurse contacts (mean difference 0.055, 95% CI 0.003 to 0.141) and use of other aids and adaptations (mean difference 0.004, 95% CI 0.001 to 0.007). For survivors to hospital discharge (see *Appendix 1*, *Table 30*), there were noticeable differences in resource use for district nurse contacts (mean difference 2.494, 95% CI 0.013 to 6.315) only. For all other resource use items, no differences between the trial arms were apparent.

In terms of non-NHS/PSS resource use, encompassing expenditure incurred by patients, family members and lost income due to ill health as a result of the cardiac arrest, for all participants at 3 months (see *Appendix 1*, *Table 27*), no significant differences were observed during this time period. There were also no significant differences in non-NHS/PSS resource use for survivors to hospital discharge over this period (see *Appendix 1*, *Table 31*).

Between 3 and 6 months post randomisation, and for all participants (see *Appendix 1*, *Table 29*), differences in resource use from a broader perspective were observed for reliance on child care (mean difference 0.004 occurrences, 95% CI 0.001 to 0.007 occurrences), travel costs (mean difference 0.01, 95% CI 0.000 to 0.019) and other additional costs (mean difference 0.014, 95% CI 0.000 to 0.027). For survivors to hospital discharge (see *Appendix 1*, *Table 31*), there were no noticeable differences between the two trial arms for all other resource use items.

Unit costs

Unit costs, and data sources from which they were derived, of resource use variables are presented in *Appendix 1*, *Table 32*. The unit cost of emergency ambulance (including vehicle and crew) support was estimated at £8.80 per minute in 2017 prices. This was based on a 2008 estimate of £6.80 per minute of emergency ambulance response reported in the *Unit Costs of Health and Social Care 2008*[160] compendium, published by the Personal Social Services Research Unit, and inflated to reflect the Hospital and Community Health Service pay and price inflation reported in the *Unit Costs of Health and Social Care 2017*.[140] The total cost of prehospital emergency response was calculated for each patient using the following formula:

$$(\text{Number of vehicles in attendance} \times \text{time spent at scene} + \text{time taken to hospital and/or mortuary} + 60) \times \text{cost per minute of emergency ambulance.} \quad (1)$$

Unit cost values and their sources are reported for all other resource inputs in *Appendix 1*, *Table 32*.

Economic cost estimates at level of resource use variable and category, trial data collection instruments

Tables 16 (all patients) and *17* (survivors) summarise the estimated economic costs for hospital- and community-based health and social care services (NHS/PSS costs), based on the CRF data by trial allocation, resource category and trial period. The equivalent, more disaggregated, information at the level of resource variables is presented in *Appendix 1* (see *Table 33* for NHS/PSS costs for all patients and *Table 35* for NHS/PSS costs for survivors; see *Table 34* for non-NHS/PSS costs for all patients and *Table 36* for non-NHS/PSS costs for survivors). Economic costs from an NHS and PSS perspective for all participants are presented in *Table 16* by trial arm, trial period and cost category. Between randomisation and 3 months post randomisation, the mean total emergency response costs were, on average, higher for the adrenaline arm than for the placebo arm: £1716 versus £1660, respectively (mean cost difference £56.41, 95% bootstrapped CI £18.54 to £94.42). Similarly, total inpatient costs were higher, on average, for the adrenaline arm than for the placebo arm: £2094 versus £1082 (mean cost difference £1011.78, 95% bootstrapped CI £729.39 to £1325.13). This was driven by higher costs for ED costs, general ward stays (£129 vs. £80 for the adrenaline vs. placebo arms, respectively; mean difference £49.19, 95% CI £13.40 to £87.45) and ICU stays (£1924 vs. £998 for the adrenaline vs. placebo arms, respectively; mean difference £926.88, 95% CI £629.78 to £1250.56) (see *Appendix 1*, *Table 33*). There were no significant differences in costs from an NHS and PSS perspective for survivors to hospital discharge at 3 months (see *Table 17*).

Between 3 and 6 months, for all participants (see *Table 16*), the mean total primary health-care costs were significantly higher for the adrenaline arm (£6.54) than for the placebo arm (£1.55) (mean cost difference £4.99, 95% bootstrapped CI £1.36 to £9.26). Medications costs were, on average, significantly higher for the adrenaline arm (£3.68) than for the placebo arm (£1.03) (mean cost difference £2.65, 95% bootstrapped CI £0.71 to £5.61). For survivors to hospital discharge (see *Table 17*), the mean total primary health-care costs were significantly higher for the adrenaline arm (£312) than for the placebo arm (£125) (mean cost difference £187, 95% bootstrapped CI £29.94 to £378.04).

Economic costs from a broader societal perspective are presented in *Appendix 1* (see *Table 34* for all participants and *Table 36* for survivors) by trial arm, trial period and cost category. There were no significant differences in costs for the period between randomisation and 3 months (see *Appendix 1*, *Table 34*). There were also no noticeable differences in the costs when looking at the information for survivors to hospital discharge (see *Appendix 1*, *Table 36*). Between 3 and 6 months post randomisation, for all participants (see *Appendix 1*, *Table 34*), mean total additional health-care-related costs (out-of-pocket medical expenditure on items such as over-the-counter medications, travel to medical appointments and aids) and non-health-care costs (e.g. child care and lost income as a result of the cardiac arrest) were, on average, significantly higher for the adrenaline group (£18.52) than for the placebo group (£5.02) (mean cost difference £13.50, 95% bootstrapped CI £0.43 to £33.45).

Total economic cost estimates over trial follow-up, and trial data collection instruments

Total costs estimated based on the trial data collection instruments for all participants are presented in *Table 18* by trial arm, trial period and aggregate cost category. Based on total costs, adrenaline was, on average, more costly. Between randomisation and 3 months, the total mean cost was higher, from an NHS and PSS perspective, for the adrenaline arm than for the placebo arm: £3765 versus £2687, respectively (mean cost difference £1078, bootstrapped 95% CI £790 to £1406). This was also the case when costs were considered from a broader societal perspective: £3774 versus £2698 for the adrenaline and placebo arms, respectively (mean cost difference £1076, bootstrapped 95% CI £782 to £1403). There were no significant differences between the trial arms in total mean costs for survivors to hospital discharge (*Table 19*). Between 3 and 6 months, for all participants, the total mean non-NHS/PSS costs

TABLE 16 Total NHS and PSS costs (2017 prices) by trial arm, all participants, based on resource use collected through trial CRF data only

		Adrenaline arm ($N = 4015$)		Placebo arm ($N = 3999$)		Adrenaline vs. placebo	
Post-randomisation assessment period	Category	Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
0–3 months	Emergency response costs	4010	1716.03 (17.05)	3992	1659.61 (10.41)	56.41 (18.54 to 94.42)	< 0.001
	Intervention costs	4008	33.82 (0.27)	3990	0 (0)	33.82 (33.27 to 34.32)	< 0.001
	Inpatient costs	3964	2093.96 (128.43)	3967	1082.18 (88.63)	1011.78 (729.39 to 1325.13)	< 0.001
	Outpatient costs	3967	18.62 (5.63)	3961	10.63 (3.38)	8 (–3.77 to 21.61)	0.196
	Community care costs	3976	10.69 (4.76)	3969	5.42 (1.67)	5.27 (–2.75 to 17.05)	0.308
	Medication costs	3975	6.8 (1.7)	3970	4.98 (1.68)	1.82 (–2.96 to 6.61)	0.45
	Aids and adaptations costs	3967	1.78 (1.29)	3964	1.75 (1.29)	0.02 (–3.8 to 3.88)	0.972
	Total NHS and PSS costs	3937	3764.73 (127.92)	3936	2686.9 (90)	1077.83 (790.49 to 1406.45)	< 0.001
3–6 months	Inpatient costs	3961	83.1 (50.84)	3949	37.36 (19.5)	45.73 (–37.8 to 172.54)	0.388
	Outpatient costs	3960	18.59 (6.93)	3949	9.25 (4.02)	9.34 (–4.73 to 25.67)	0.218
	Community care costs	3964	6.54 (2.03)	3953	1.55 (0.33)	4.99 (1.36 to 9.26)	< 0.001
	Medication	3961	3.68 (1.2)	3952	1.03 (0.26)	2.65 (0.71 to 5.61)	0.002
	Aids and adaptations costs	3959	4.78 (2.18)	3954	1.24 (1.09)	3.54 (–1 to 8.89)	0.12
	Total NHS and PSS costs	3948	93.75 (50.8)	3940	47.62 (20.86)	46.13 (–38.68 to 169.18)	0.382
0–6 months	Total NHS and PSS costs	3919	3641.84 (149.13)	3914	2548.36 (84)	1093.49 (800.43 to 1442)	< 0.001

SE, standard error.

Note

The CIs were obtained via the bootstrapped percentile method.

TABLE 17 NHS and PSS costs (2017 prices) by trial arm, survivors to hospital discharge, CRF data

Assessment period	Category	Adrenaline arm (*N* = 128)		Placebo arm (*N* = 91)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (bootstrap 95% CI) (£)	*p*-value
0–3 months after randomisation	Emergency response costs	127	1535.32 (45.62)	91	1455.87 (53.8)	79.45 (–51.87 to 222.5)	0.242
	Intervention costs	128	14.38 (0.99)	91	0 (0)	14.38 (12.44 to 16.33)	< 0.001
	Inpatient costs	88	29,425.72 (3032.74)	65	24,356.65 (3055.72)	5069.07 (–3985.61 to 13,777.15)	0.244
	Outpatient costs	86	859.01 (241.89)	57	738.40 (214.69)	120.61 (–494.23 to 763.48)	0.7
	Community care costs	95	447.36 (204.33)	65	330.81 (89.27)	116.55 (–250.21 to 580.86)	0.684
	Medications	94	287.66 (64.88)	66	299.49 (93.53)	–11.83 (–250.68 to 183.9)	0.97
	Aids and adaptations costs	86	81.91 (63.42)	60	115.82 (84.33)	–33.91 (–263.39 to 159.46)	0.736
	Total NHS and PSS costs	72	32,669.22 (3589.54)	50	27,956.52 (3795.11)	4712.7 (–5527.48 to 14,967.31)	0.382
3–6 months after randomisation	Inpatient costs	80	4114.25 (2466.27)	45	1916.46 (957.58)	2197.79 (–2031.75 to 8385.56)	0.44
	Outpatient costs	79	932.02 (328.67)	45	812.04 (331.92)	119.97 (–835.56 to 1002.03)	0.736
	Community care costs	83	312.26 (86.32)	49	125.27 (19.78)	187 (29.94 to 378.04)	0.02
	Medications	80	182.04 (54.94)	48	84.86 (18.07)	97.18 (2.60 to 225.3)	0.044
	Aids and adaptations costs	78	242.69 (104.76)	50	97.99 (87.6)	144.7 (–117.87 to 409.13)	0.296
	Total NHS and PSS costs	67	5524.18 (2914.88)	36	3508.31 (1334.03)	2015.87 (–3297.29 to 8742.91)	0.598
0–6 months	Total NHS and PSS costs	54	33,385.85 (7293.82)	29	29,144.43 (4609.34)	4241.42 (–9982.79 to 22,538.49)	0.698

SE, standard error.

Note

The CIs were obtained via the bootstrapped percentile method.

TABLE 18 Total costs (2017 prices) by trial arm, all participants, CRF data

		Adrenaline arm ($N = 4015$)		Placebo arm ($N = 3999$)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean cost difference (bootstrap 95% CI) (£)	*p*-value
0–3 months post randomisation	Total NHS and PSS costs	3937	3764.73 (127.92)	3936	2686.9 (90)	1077.83 (790.49 to 1406.45)	< 0.001
	Total non-NHS and PSS costs	3973	37.34 (10.32)	3970	19.93 (6.45)	17.4 (−6.71 to 40.77)	0.156
	Total societal costs	3936	3774.22 (127.5)	3936	2698.06 (91.12)	1076.16 (782.48 to 1403.42)	< 0.001
3–6 months post randomisation	Total NHS and PSS costs	3948	93.75 (50.8)	3940	47.62 (20.86)	46.13 (−38.68 to 169.18)	0.382
	Total non-NHS and PSS costs	3962	18.51 (8.13)	3953	4.95 (2.25)	13.56 (0.49 to 33.62)	0.038
	Total societal costs	3948	110.4 (52.28)	3939	46.22 (20.39)	64.18 (−21.67 to 188.32)	0.192
0–6 months post randomisation	Total NHS and PSS costs	3919	3641.84 (149.13)	3914	2548.36 (84)	1093.49 (800.43 to 1442)	< 0.001
	Total non-NHS and PSS costs	3956	50.84 (14.62)	3952	15.07 (5.59)	35.77 (8.1 to 68.61)	0.01
	Total societal costs	3919	3671.5 (150.28)	3913	2535.36 (82.89)	1136.14 (840.32 to 1484.33)	< 0.001

SE, standard error.

Note

The CIs were obtained via the bootstrapped percentile method.

TABLE 19 Total costs (2017 prices) by trial arm, survivors to hospital discharge, CRF data

		Adrenaline arm ($N = 128$)		Placebo arm ($N = 91$)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean cost difference (bootstrap 95% CI) (£)	*p*-value
0–3 months post randomisation	Total NHS and PSS costs	72	32,669.22 (3589.54)	50	27,956.52 (3795.11)	4712.7 (–5527.48 to 14,967.31)	0.382
	Total non-NHS and PSS costs	92	1612.33 (420.67)	66	1199 (372.51)	413.33 (–686.8 to 1566.93)	0.444
	Total societal costs	71	33,602.52 (3614.7)	50	28,835.07 (3848.78)	4767.45 (–5096.05 to 15,071.74)	0.394
3–6 months post randomisation	Total NHS and PSS costs	67	5524.18 (2914.88)	36	3508.31 (1334.03)	2015.87 (–3297.29 to 8742.91)	0.598
	Total non-NHS and PSS costs	81	905.61 (372.83)	49	399.36 (174.22)	506.25 (–196.78 to 1464.21)	0.204
	Total societal costs	67	6505.26 (3014.44)	35	3450.12 (1332.71)	3055.14 (–2433.59 to 9949.4)	0.374
0–6 months post randomisation	Total NHS and PSS costs	54	33,385.85 (7293.82)	29	29,144.43 (4609.34)	4241.42 (–9982.79 to 22,538.49)	0.698
	Total non-NHS and PSS costs	75	2681.64 (703.79)	49	1215.1 (432.91)	1466.54 (–171.05 to 3200.25)	0.082
	Total societal costs	54	35,538.15 (7286.24)	28	28,277.49 (4592.94)	7260.66 (–6800.38 to 24,616)	0.422

SE, standard error.

Note

The CIs were obtained via the bootstrapped percentile method. This table contains NHS Digital data. Copyright © 2019, the Health and Social Care Information Centre. Re-used with the permission of the Health and Social Care Information Centre [and/or [name of licensor]]. All rights reserved.

were significantly higher for the adrenaline arm (£18.51) than for the placebo arm (£4.95) (mean cost difference £13.56, bootstrapped 95% CI £0.49 to £33.62). There were no significant differences between the trial arms in total mean costs for survivors to hospital discharge (see *Table 19*). Over the trial time horizon of the first 6 months post randomisation, for all participants, adrenaline was, on average, more costly (see *Table 18*). The total mean cost from an NHS and PSS perspective was higher for the adrenaline arm than for the placebo arm: £3642 versus £2548, respectively (mean cost difference £1093, bootstrapped 95% CI £800 to £1442). This was also the case when costs were considered from a broader societal perspective: £3672 versus £2535 for the adrenaline and placebo arms, respectively (mean cost difference £1136, bootstrapped 95% CI £840 to £1484). There were no differences between the groups for total mean costs for survivors to hospital discharge (see *Table 19*).

Economic cost estimates, combined Hospital Episode Statistics and trial instrument data in the 0–6 months post-randomisation period

Economic costs from an NHS and PSS perspective for all participants based on combining resource use data from HES and trial instrument sources are presented in *Table 20* by trial arm, cost period and cost category. For the whole trial population, HES data were used to estimate only the cost of hospital-based services (inpatient admissions and ED and outpatient attendances) during the period 0–6 months after randomisation for 1833 (45.7%) of the 4015 participants in the adrenaline arm and 1094 (27.4%) of the 3999 participants in the placebo arm. Hospitalisation costs for the remaining participants were either set at zero (primarily as a result of patients dying at the scene of cardiac arrest: adrenaline, $n = 1985$; placebo, $n = 2768$) and trial CRFs completed by paramedics and trial participants (adrenaline, $n = 188$ and placebo, $n = 126$), with any remaining hospitalisation costs classed as missing (adrenaline, $n = 9$ and placebo, $n = 11$). Non-hospital-based costs of health and social care services were estimated from resource use data collected using economic questionnaires completed by trial participants.

Between randomisation and 6 months (see *Table 20*), the total mean cost estimates based on the combined HES and trial data collection instrument data were higher, from an NHS and PSS perspective, for the adrenaline arm (£3789) than for the placebo arm (£2698) (mean cost difference £1091, bootstrapped 95% CI £807 to £1398). This was also the case when costs were considered from a broader societal perspective: £3829 versus £2687 for the adrenaline and placebo arms, respectively (mean cost difference £1143, bootstrapped 95% CI £861 to £1451).

There were no significant differences in total mean costs for survivors to hospital discharge between trial arms (*Table 21*). Over the trial time horizon of 6 months, for all participants, the adrenaline intervention was, on average, more costly, but the difference in total costs was not statistically significant. The mean total cost was higher, from an NHS and PSS perspective, for the adrenaline arm (£33,554) than for the placebo arm (£33,348) (mean cost difference £205, bootstrapped 95% CI −£10,849 to £10,159). This was also the case when costs were considered from a broader societal perspective: £34,994 versus £31,557 for the adrenaline and placebo arms, respectively (mean cost difference £3438, bootstrapped 95% CI −£7222 to £13,343).

Economic costs, combined Hospital Episode Statistics and trial data collection form based resource use data, 12-month period from randomisation

Cost estimates covering the 1-year period from randomisation are also presented in *Table 20* (whole trial population) and *Table 21* (survivors to hospital discharge) by trial allocation and resource category. These costs were derived using the methodology described in *Chapter 4*, *Estimation of costs for the total 1-year period after randomisation*, taking into account the fact that not all patients had complete HES-derived hospital care data covering the 1-year period from randomisation.

TABLE 20 Total costs (2017 prices) by trial arm, combined HES and CRF data, all participants

		Adrenaline arm ($N = 4015$)		Placebo arm ($N = 3999$)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean cost difference (bootstrap 95% CI) (£)	*p*-value
0–6 months	Hospitalisation costs (NHS and PSS)	4006	2669 (179)	3988	1460 (129)	1209 (804 to 1660)	< 0.001
	Non hospitalisation costs (NHS and PSS)	3934	1785 (21)	3926	1678 (13)	107 (61 to 155)	< 0.001
	Non-NHS and PSS costs	3956	51 (15)	3952	15 (6)	36 (8 to 69)	0.01
	Total NHS and PSS costs	3934	3789 (121)	3926	2698 (94)	1091 (807 to 1398)	< 0.001
	Total societal costs	3933	3829 (124)	3925	2687 (92)	1143 (861 to 1451)	< 0.001
0–12 months[a]	Hospitalisation costs (NHS and PSS)	3971	2419 (173)	3961	1322 (131)	1096 (692 to 1537)	< 0.001
	Non hospitalisation costs (NHS and PSS)	3922	1822 (32)	3915	1677 (13)	145 (87 to 215)	< 0.001
	Non-NHS and PSS costs	3941	63 (26)	3939	16 (8)	47 (2 to 111)	0.042
	Total NHS and PSS costs	3921	3748 (126)	3915	2651 (95)	1096 (804 to 1415)	< 0.001
	Total societal costs	3920	3793 (132)	3915	2662 (96)	1131 (820 to 1473)	< 0.001

SE, standard error.

a The 12-month costs for patients with < 12 months of complete HES data (adrenaline arm, $n = 31$; placebo arm, $n = 26$) were treated as missing observations.

Note

TABLE 21 Total costs (2017 prices) by trial arm, survivors to hospital discharge, combined HES and CRF data

		Adrenaline arm, ($N = 128$)		Placebo arm, ($N = 91$)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (n)	Mean cost (SE) (£)	Participants with complete data (n)	Mean cost (SE) (£)	Mean cost difference (bootstrap 95% CI) (£)	p-value
0–6 months	Hospitalisation costs (NHS and PSS)	123	37,153 (3780)	83	33,258 (3162)	3894 (–5364 to 14,798)	0.408
	Non-hospitalisation costs (NHS and PSS)	64	3467 (686)	39	3011 (645)	456 (–1357 to 2388)	0.58
	Non-NHS and PSS costs	75	2682 (716)	49	1215 (429)	1467 (–91 to 3115)	0.07
	Total NHS and PSS costs	64	33,554 (2956)	39	33,348 (4263)	205 (–10,849 to 10,159)	0.9
	Total societal costs	63	36,522 (3211)	38	32,988 (4153)	3534 (–7106 to 13,535)	0.49
0–12 months[a]	Hospitalisation costs (NHS and PSS)	89	39,577 (5273)	57	38,447 (4801)	1130 (–11,842 to 15,807)	0.856
	Non-hospitalisation costs (NHS and PSS)	52	6671 (1978)	28	3432 (927)	3240 (–656 to 7924)	0.11
	Non-NHS and PSS costs	60	4150 (1641)	36	1756 (799)	2394 (–748 to 6580)	0.152
	Total NHS and PSS costs	51	37,962 (4448)	28	38,868 (6258)	–906 (–17,196 to 13,318)	0.982
	Total societal costs	50	42,204 (5143)	28	40,401 (6340)	1804 (–15,835 to 16,999)	0.766

SE, standard error.

a The 12-month costs for patients with < 12 months of complete HES data (adrenaline arm, $n = 31$; placebo arm, $n = 26$) were treated as missing observations.

Note

The CIs were obtained via the bootstrapped percentile method. This table contains NHS Digital data.

Between randomisation and 12 months, and for the whole trial population, the estimated total mean costs based on complete cases from the combined HES and trial data collection instrument data were higher, from an NHS and PSS perspective, for the adrenaline arm (£3748) than for the placebo arm (£2651) (mean total cost difference £1096, bootstrapped 95% CI £804 to £1415). This was also the case when costs were considered from a broader societal perspective: £3793 versus £2662 for the adrenaline and placebo arms, respectively (mean total cost difference £1131, bootstrapped 95% CI £820 to £1473). There were no significant differences in total mean costs between the trial arms for survivors to hospital discharge (see *Table 21*) during the first 12 months after randomisation. During this period, adrenaline was, on average, associated with increased costs, but the difference in total costs was not statistically significant.

Health-related quality-of-life and quality-adjusted life-year outcomes

The distribution of the responses to the EQ-5D-5L and SF-12 health-related quality-of-life questionnaires by trial arm and trial period for survivors to hospital discharge are presented in *Appendix 1*, *Tables 37* and *38*, respectively. The comparisons of responses were conducted on the basis of optimal level of function (e.g. 'no problem' on the EQ-5D-5L) versus suboptimal level of function (indicating any functional impairment). At the 3-month assessment point, the only statistically significant differences in levels of function in health-related quality of life was for the self-care dimension of the EQ-5D-5L ($p = 0.020$). There were no statistically significant differences in levels of function in health-related quality of life for participant-reported dimensions of the EQ-5D-5L or SF-12 measures between the adrenaline and placebo groups at the 6-month assessment point (see *Appendix 1*, *Tables 37* and *38*).

The mean health utility scores from alternative sources [mRS mapped to the EQ-5D, EQ-5D-5L and SF-6D (derived from the SF-12)] by trial arm and trial period for all participants are presented in *Tables 22* and *23*, and displayed in *Appendix 1*, *Figure 25* (utility generated via the mRS and EQ-5D-5L). There were no statistically significant differences in mean utility scores between the adrenaline arm and placebo arm for the health utility scores from different sources at the trial assessment points. However, the mean health utility scores, based on mRS mapping to the EQ-5D-3L for survivors to hospital discharge (see *Table 23*), were statistically significantly lower at hospital discharge for the adrenaline arm (0.48) than for the placebo arm (0.60) (unadjusted mean difference −0.118, 95% CI −0.196 to −0.032).

Cost-effectiveness results

Base-case analysis

The incremental cost-effectiveness of adrenaline is shown in *Table 24* for the participants with costs and health outcomes data subject to multiple imputation. When an NHS and PSS perspective was adopted (i.e. that adopted for the baseline analysis), and health outcomes were measured in terms of QALYs based on the EQ-5D and mRS measures, the adjusted mean total cost was £3591 for the adrenaline arm, and £2285 for the placebo arm, generating a mean incremental cost of £1306 (95% CI £837 to £1774) over the first 6-month post-randomisation period. The adjusted mean QALYs was 0.0025 in the adrenaline arm and 0.0017 in the placebo arm, generating a mean difference in QALYs of 0.0008 (95% CI −0.0014 to 0.003). The ICER was £1,693,003. The probability that adrenaline was cost-effective at a cost-effectiveness threshold of £30,000 per QALY gained was zero. Extending the within-trial analysis to cover the 1-year period from randomisation by extrapolating costs and utilities measured at 6 months to 12 months reduced the base-case ICER from £1,693,003 per QALY gained to £644,308 per QALY gained for adrenaline, compared with placebo (mean incremental costs of £1411 and mean incremental QALYs of 0.0022). Extrapolating the within-trial analysis to cover the lifetime of survivors (see the model described in *Chapter 4*, *Extrapolating beyond trial follow-up*) reduced the ICER further to £81,070 per QALY gained (mean incremental costs of £1775 and mean incremental QALYs of 0.022).

TABLE 22 Health utilities: all patients

		Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (*n*)	Mean (SE) utility (£)	Participants with complete data (*n*)	Mean (SE) utility (£)	Mean difference (bootstrapped 95% CI) utility (£)	*p*-value
Hospital discharge	mRS mapped to EQ-5D	4009	0.015 (0.002)	3994	0.013 (0.002)	0.002 (−0.002 to 0.006)	0.582
0–3 months after randomisation	EQ-5D-5L	3976	0.013 (0.002)	3970	0.011 (0.001)	0.002 (−0.002 to 0.006)	0.472
	mRS mapped to EQ-5D	3991	0.016 (0.002)	3981	0.012 (0.002)	0.003 (−0.001 to 0.008)	0.228
	SF-12 (SF-6D)	3968	0.013 (0.002)	3968	0.011 (0.001)	0.002 (−0.002 to 0.007)	0.406
3–6 months post randomisation assessment period	EQ-5D-5L	3963	0.011 (0.002)	3976	0.008 (0.001)	0.002 (−0.002 to 0.006)	0.420
	mRS mapped to EQ-5D	3993	0.015 (0.002)	3975	0.011 (0.001)	0.004 (0 to 0.009)	0.118
	SF-12 (SF-6D)	3963	0.012 (0.001)	3955	0.008 (0.001)	0.004 (0 to 0.007)	0.092

TABLE 23 Health utilities: survivors to hospital discharge

		Adrenaline arm (*N* = 128)		Placebo arm (*N* = 91)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (*n*)	Mean (SE) costs (£)	Participants with complete data (*n*)	Mean (SE) costs (£)	Mean difference (bootstrapped 95% CI) costs (£)	*p*-value
Hospital discharge	mRS mapped to EQ-5D	126	0.479 (0.031)	89	0.597 (0.029)	−0.118 (−0.196 to -0.032)	0.002
0–3 months after randomisation	EQ-5D-5L	95	0.533 (0.039)	66	0.643 (0.038)	−0.11 (−0.211 to 0.004)	0.056
	mRS mapped to EQ-5D	109	0.576 (0.032)	76	0.651 (0.033)	−0.075 (−0.163 to 0.016)	0.104
	SF-12 (SF-6D)	86	0.609 (0.022)	64	0.669 (0.021)	−0.06 (−0.116 to 0.003)	0.066
3–6 months post randomisation	EQ-5D-5L	81	0.517 (0.046)	51	0.648 (0.051)	−0.131 (−0.257 to 0.01)	0.064
	mRS mapped to EQ-5D	111	0.538 (0.035)	70	0.62 (0.037)	−0.082 (−0.181 to 0.021)	0.116
	SF-12 (SF-6D)	80	0.584 (0.026)	51	0.634 (0.027)	−0.05 (−0.116 to 0.026)	0.202

TABLE 24 Main cost-effectiveness results (2017 prices)

	Adrenaline arm, mean (SE)		Placebo arm, mean (SE)		Mean difference (95% CI)		Cost-effectiveness		
Analysis model	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)[a]	QALYs[a]	ICER (£/QALY)	INMB at £30,000/QALY[b] (95% CI (£))	Probability of being cost-effective at £30,000/QALY[b]
Within-trial base case (adjusted[c] multiple imputation), 6 months post cardiac arrest event	3591 (540)	0.0025 (0.0025)	2285 (544)	0.0017 (0.0025)	1306 (837 to 1774)	0.0008 (−0.0014 to 0.003)	1,693,003	−1282 (−1733 to −831)	0
Extrapolation to 12 months post cardiac arrest event	3741 (536)	0.006 (0.0049)	2330 (541)	0.0038 (0.005)	1411 (946 to 1876)	0.0022 (−0.0021 to 0.0065)	644,308	−1346 (−1784 to −907)	0
Extrapolation to lifetime horizon (decision-analytic model)	5308 (797)	0.111 (0.037)	3534 (736)	0.089 (0.031)	1775 (250 to 3394)	0.022 (−0.011 to 0.063)	81,070	−1118 (−2776 to 487)	0.098

INMB, incremental net monetary benefit; SE, standard error.

a Difference in mean costs and mean QALYs between adrenaline and placebo groups, 95% confidence intervals in brackets.

b Probability that the intervention is cost-effective at willingness-to-pay threshold of £30,000 per QALY gained, based on 1000 Monte Carlo simulations.

c Adjusted analyses were adjusted for patients' age, sex, interval between emergency call and ambulance arrival at scene, interval between ambulance arrival at scene and administration of the trial agent, initial cardiac rhythm, cause of cardiac arrest, whether or not the cardiac arrest was witnessed and whether or not a bystander performed CPR.

Note

Mean costs and QALYs are estimated at the mean age of 60 years and for categorical values at the baseline covariate group (sex = female, not witnessed, ambulance arrived in < 10 minutes from receiving 999 call, first dose administered in < 10 minutes from arrival at scene, initial rhythm is shockable, aetiology = medical and bystander CPR = yes).

Incremental net monetary benefits

The associated adjusted mean incremental net monetary benefits (INMBs) of adrenaline at cost-effectiveness thresholds of £30,000 per QALY were as follows: –£1282 for the within-trial base-case analysis (adjusted multiple imputation), 6 months post cardiac arrest event; –£1346 for extrapolation to 12 months post cardiac arrest event; and –£1118 for extrapolation to a lifetime time horizon (decision-analytic model) (see *Table 24*). The base-case mean INMB was < £0, suggesting that adopting the adrenaline protocol would result in a net economic loss of £1258, on average, from an NHS and PSS perspective [INMB –£1250 (95% CI –£1686 to –£815) at 6 months and –£1118 (95% CI –£2776 to £487) over the lifetime of survivors, assuming a cost-effectiveness threshold of £30,000 per QALY]. The CEAC shows that this results in a probability of cost-effectiveness of < 1% at cost-effectiveness thresholds of < £200,000 (see *Appendix 1*, *Figure 25*); that is, if decision-makers are willing to pay £30,000 for an additional QALY, the probability that adrenaline is cost-effective remains < 1% over the 6-month base-case within-trial time horizon and 11% over a lifetime time horizon (see *Table 24*).

Sensitivity analysis

Several sensitivity analyses were undertaken to assess the impact of uncertainty surrounding key parameters or methodological features on the cost-effectiveness results. The base-case analyses were replicated using Stata software and the results were consistent with the primary analyses. The adjusted and unadjusted complete-case analyses also exhibit the same pattern of results as the base-case analyses (see *Appendix 1*, *Table 39*). The probability that adrenaline is cost-effective remained relatively static (at about 0%) for the majority of the sensitivity analyses (i.e. societal costs, QALYs based on the mRS, 12-month time horizon, 12-month time horizon and societal perspective, and 12-month time horizon and QALYs based on the mRS). All sensitivity analyses showed that the average INMB value always remains < £0 (see *Appendix 1*, *Table 39*).

In sensitivity analyses that explored the impact of the missing not at random assumption on the within-trial base-case results, imputed utility values and costs were systematically decreased and increased while holding imputed values for other variables constant. The results are displayed in *Appendix 1*, *Tables 40* and *41*. They suggest that doubling the value of imputed utilities favoured adrenaline (the ICER decreased to £1,021,684 per QALY), whereas halving them favoured placebo (the ICER increased to £2,067,739 per QALY gained). Similarly, doubling imputed costs favoured adrenaline and decreased the ICER to £1,186,037 per QALY, whereas halving them had little effect on the within-trial base-case cost-effectiveness results (£1,688,008 per QALY). The probability that adrenaline is cost-effective was zero at cost-per-QALY thresholds of < £100,000 across alternative assessments, in which missing values for the main economic costs and outcomes were not assumed to be missing at random (see *Appendix 1*, *Figures 28* and *29*).

Subgroup analyses

To explore the heterogeneity in the cost-effectiveness results, 10 variables were considered: cause of cardiac arrest (medical, non-medical), age (≤ 60 years, > 60 years), sex (female, male), time from EMS arrival at scene to administration of first dose (≤ 10 minutes, > 10 minutes), time from 999 call received to EMS arrival at scene (≤ 10 minutes, > 10 minutes), shockable rhythm (yes, no), number of syringes given out of two (≤ 2, > 2), number of syringes given out of four (≤ 4, > 4), witnessed by (not witnessed, EMS, bystander), and bystander CPR (no, yes, unknown). All subgroup analyses were based on the patient-reported EQ-5D and mRS measures and used multiple imputation and covariate adjustments, as per the primary analyses (see *Appendix 1*, *Table 42*). Subgroups for which the probability of cost-effectiveness was > 10% at £30,000 per QALY gained over the 6 months within-trial time horizon were cardiac arrest of medical aetiology (probability of cost-effectiveness 15%), EMS witnessed (15%), aged > 60 years (20%), two or more doses of adrenaline administered (27%) and four or more doses of adrenaline administered (32%). All other subgroups generated probabilities of cost-effectiveness for adrenaline of < 10% at a cost-effectiveness threshold of £30,000 per QALY gained.

Secondary health economic outcomes

Results are presented in *Table 25* for the cost-effectiveness of adrenaline expressed as incremental cost per unit increase in the proportion surviving to 6 months post cardiac arrest and the proportion surviving with good neurological function (i.e. neurologically intact survivor). The adjusted mean cost over 6 months was £3654 in the adrenaline arm and £2284 in the placebo arm, generating a cost-difference of £1370 (95% bootstrapped CI £954 to £1840). The 6-month adjusted survival probability was 0.0051 in the adrenaline arm and 0.0037 in the placebo arm, generating a difference in survival probability of 0.0014 (95% CI −0.0003 to 0.003) in favour of adrenaline. The 6-month adjusted probability of survival with good functional outcome was 0.0026 for adrenaline and 0.0023 for placebo, generating a difference in probability of 0.0014 (95% CI −0.0003 to 0.003) in favour of adrenaline. The ICER was £982,880 per percentage point increase in overall survival and £3,772,322 per percentage point increase in neurological survival.

TABLE 25 Cost-effectiveness results, secondary health economic outcomes (2017 prices)

	Adrenaline arm, mean (SE)		Placebo arm, mean (SE)		Mean difference (bootstrapped 95% CI)		Cost-effectiveness		
Outcome	Costs (£)	Probability	Costs (£)	Probability	Costs (£)	Probability	ICER (£)	INMB at £30,000/QALY (95% CI) (£)	Probability of being cost-effective at £30,000/QALY
6 months' survival	3654 (388)	0.0051 (0.0022)	2284 (420)	0.0037 (0.0016)	1370 (954 to 1840)	0.0014 (–0.0003 to 0.003)	982,880	–1328 (–1794 to –935)	0
6 months' neurologically intact survival	3654 (388)	0.0026 (0.0022)	2284 (420)	0.0023 (0.0016)	1370 (954 to 1840)	0.0004 (–0.0003 to 0.003)	3,772,322	–1359 (–1794 to –935)	0

INMB, incremental net monetary benefit; SE, standard error.

Chapter 6 Discussion

Overall evidence

The use of adrenaline during resuscitation for OHCA resulted in a significantly higher rate of survival to hospital admission (23.6% vs. 8.0% for the adrenaline and placebo arms, respectively; aOR 3.83, 95% CI 3.30 to 4.43) than the use of placebo. Thirty-day survival was also higher (3.2% vs. 2.4% for the adrenaline and placebo arms, respectively; aOR 1.47, 95% CI 1.09 to 1.97), but the rate of favourable neurological outcome was not significantly different (2.2% vs. 1.9% for the adrenaline and placebo arms, respectively; aOR 1.19, 95% CI 0.85 to 1.68). The pattern of improved survival but no significant improvement in neurological outcomes continued through to 6 months. By 12 months, survival in the adrenaline arm was 1.5%, compared with 1% in the placebo arm (aOR 1.40, 95% CI 1.00 to 1.96). A Bayesian analysis found that the probability that the risk difference for survival was > 1%, favouring the adrenaline arm, was 37%, and the probability that favourable neurological outcome was improved by > 1% was 1.9%. An adjusted subgroup analysis did not identify a significant interaction for any of the subgroups studied.

More survivors in the adrenaline group than in the placebo group had severe neurological impairment at hospital discharge. The number with severe neurological impairment decreased through to 6 months, although evaluation was limited by greater loss to follow-up. Examining health-related quality of life up to 6 months after randomisation, and cognitive function, anxiety/depression or post-traumatic stress to 3 months, showed significant functional impairment in cardiac arrest survivors, compared with the normal population. One-third to half of patients reported needing help from someone for everyday activities. For the majority, this was a new situation after their cardiac arrest. Fewer than half reported having made a full mental recovery after their cardiac arrest. Although underpowered, the pattern of impairment suggested greater disability in the adrenaline group.

The ICER for adrenaline was estimated at £1,693,003 per QALY gained over the first 6 months after the cardiac arrest event and £81,070 per QALY gained over a lifetime time horizon. The associated adjusted mean INMBs of adrenaline at a cost-effectiveness threshold of £30,000 per QALY gained was –£1282 at 6 months and –£1118 over a lifetime of survivors, suggesting that adopting the adrenaline protocol would result in a net economic loss. The CEAC shows that these INMBs result in a probability of cost-effectiveness of < 1% for cost-effectiveness thresholds of < £200,000 for an additional QALY over a time horizon of up to 1 year after the cardiac arrest. Over the lifetime of survivors, the probability of cost-effectiveness approaches 50% at a £100,000 per QALY cost-effectiveness threshold.

Interpretation of results

Clinical outcomes

The use of adrenaline, in comparison with placebo, resulted in almost four times the number of patients being admitted to hospital after OHCA. This finding is broadly consistent with the findings of the PACA trial,[56] which documented an OR of 3.4 (95% CI 2.0 to 5.6) for ROSC in favour of adrenaline over placebo for OHCA.

Many more patients in the adrenaline group than in the placebo group were admitted to hospital but did not survive to discharge: 2016 (50.2%) and 1209 (30.2%) patients in the adrenaline and placebo arms, respectively, were admitted, and 128 (3.2%) and 91 (2.3%) patients in the adrenaline and placebo arms, respectively, survived to discharge. Thus, 1888 patients in the adrenaline arm died in hospital, compared with 1118 in the placebo arm. We do not have data on the mode of death,

but the majority of deaths occurred in the ED. These early deaths are more likely to be caused by circulatory failure or limitation of treatment due to the presence of severe comorbidities and functional impairment, as withdrawal of life-sustaining therapy resulting from perceived severe neurological injury should not normally occur until after 72 hours. However, although several studies have documented the mode of death among post-cardiac arrest patients admitted to an intensive trauma unit,[161–163] this has not been well documented for those dying in the ED.

In the adrenaline group, 414 of the 566 (73.1%) patients admitted to the ICU died there, compared with 176 of the 270 (65.1%) placebo group patients admitted to the ICU. Thus, 238 additional patients in the adrenaline group were admitted to an ICU, but died there. Surviving patients spent, on average, 7 days in intensive care and 21 days in hospital. By the time of hospital discharge, 128 (3.2%) patients were alive in the adrenaline group, compared with 91 (2.3%) in the placebo group, of whom 87 (2.2%) and 74 (1.9%), respectively, survived with a favourable neurological outcome. Although, at the time of discharge, 39 survivors in the adrenaline group and 16 in the placebo group had severe neurological injury, by 6 months, those with severe neurological injury numbered 23 and 9, respectively. It is well established that the functional status of cardiac arrest survivors can improve over the first few months and that some with the most severe neurological injury will die.[164] Ultimately, long-term follow-up at 12 months after cardiac arrest is ideal, but is challenging because of the resources required and the increasing loss to follow-up over time, which results in attrition bias. Data on 30-day survival were available for 4012 and 3995 patients in the adrenaline and placebo groups, respectively; by 6 months, these numbers had decreased to 4006 and 3991 for the adrenaline and placebo groups, respectively, representing a loss to follow-up for survival of just six and four patients, respectively. However, neurological outcome is more difficult to collect after hospital discharge. Data on neurological outcome at discharge were available for 4007 and 3994 patients in the adrenaline and placebo groups, respectively, but, by 6 months, these numbers had decreased to 3991 and 3973, respectively, which is a loss to follow-up for neurological outcome of 16 and 21 patients, respectively. A series of sensitivity analyses were undertaken to explore the potential impact of these missing data; the results of most of these were consistent with the main results.

Patients, clinicians and researchers prioritised health-related quality of life as a core outcome for evaluation following cardiac arrest.[165] In PARAMEDIC2, health-related quality of life was impaired among survivors at 3 and 6 months, compared with the UK general population, suggesting large differences between the well-being of OHCA survivors and that of the general population. Moreover, a reduction in both mental and, to a lesser extent, physical well-being was observed at 6 months, highlighting the importance of detailed assessment over the longer term. Impairment spanned physical and mental health domains, leading to reduced health utility scores. Compared with other studies,[166] the extent of functional impairment is greater, which is likely to be reflective of the PARAMEDIC2 cohort involving only patients refractory to initial attempts at resuscitation. Although there were no pronounced differences between the adrenaline and placebo groups, the overall level of impairment highlights an unmet need for this group of patients.

Meta-analyses of the PARAMEDIC2 and PACA[56] trials were, as expected, consistent with adrenaline increasing survival to hospital admission (RR 2.51, 95% CI 1.67 to 3.76; two studies, 8489 participants; an increase in the rate of ROSC at hospital admission from 83 to 209 per 1000, 95% CI 139 to 313) and survival to hospital discharge (RR 1.44, 95% CI 1.11 to 1.86; two studies, 8538 participants; an increase in survival to hospital discharge from 23 to 32 per 1000, 95% CI 25 to 42). Survival rates with a favourable neurological outcome at discharge were similar (RR 1.21, 95% CI 0.9 to 1.62; two studies, 8535 participants; an increase from 19 to 22 per 1000, 95% CI 17 to 30).[55]

A meta-analysis of the PARAMEDIC2 trial with the PACA[56] trial according to initial cardiac arrest rhythm found very low survival-to-discharge rates with an initial non-shockable rhythm, but a significant effect for adrenaline (0.39% for placebo vs. 1.03% for adrenaline; OR 2.57, 95% CI 1.36 to 4.83). For shockable rhythms, although survival rates were higher (9.43% vs. 11.66% in placebo and adrenaline

groups, respectively), the incremental effect of adrenaline was less pronounced (OR 1.26, 95% CI 0.93 to 1.71; between-group heterogeneity $p = 0.05$). A similar pattern was observed for survival to discharge with a favourable neurological outcome, but the CI for the OR crossed 1 for both shockable and non-shockable rhythms.[167]

Two explanations for the much higher rate of ROSC and survival to hospital admission with adrenaline, and yet no significant improvement in neurological outcome, are as follows: (1) the heart is much more resilient than the brain when exposed to a period of hypoxia-ischaemia – thus, the heart can be 'restarted' but the brain has already been damaged irreversibly; and (2) even though adrenaline increases coronary and cerebral perfusion pressure,[40] it may reduce microcirculatory flow in the brain.[29,66]

Minimum clinically important difference

An international survey of key respondents from 46 countries identified that the minimal clinically important difference for survival with a favourable neurological outcome is 3% (when the baseline rate for the population is 2%).[168] Other trials have used minimal clinically important differences of 1.4%,[169] 2%[56,170] or larger (6.3%).[171] The Universal Termination of Resuscitation Rule uses a false-positive threshold of 1%, whereas neuroprognostication algorithms[172] in intensive care allow a false-positive rate for a favourable neurological outcome of up to 5%.[91,173] The 6-month difference for survival (0.8%, 95% CI 0.1% to 1.5%) and survival with a favourable neurological outcome (0.5%, 95% CI –0.1% to 1.1%) fall below the thresholds set for a minimal clinically important difference in previous studies.

Clinical effectiveness in the context of the chain of survival

The chain of survival describes the system of care required to optimise survival after OHCA.[9] It comprises four links: early access (identifying cardiac arrest early and activating the emergency services), early CPR (to maintain perfusion to the brain and vital organs), early defibrillation (to restart the heart for patients with an initially shockable rhythm) and early post-resuscitation care. The primary PARAMEDIC2 trial publication[174] reported that 112 patients would need to be treated with adrenaline to prevent one death after cardiac arrest. This is substantially more than the number needed to be treated with other interventions delivered earlier in the chain of survival,[175,176] for example early recognition of cardiac arrest, number needed to treat = 11;[177] bystander CPR, number needed to treat = 15;[178] and rapid defibrillation, number needed to treat = 5.[179]

Cost-effectiveness

Economic evaluations in cardiac arrest research are relatively sparse. An economic model for public-access defibrillation reported an ICER of US$53,797 per QALY gained.[159] An economic evaluation of a mechanical chest compression device found that manual CPR dominated in health economic terms (mechanical CPR cost more and led to a reduction in QALYs, on average).[136] An extracorporeal CPR strategy in Sydney reported an ICER of €16,890 per QALY gained. A nurse-led post-cardiac arrest neurorehabilitation programme found a mean health benefit (0.04 additional QALYs) for minimal additional costs (€89), giving a 76% probability that the intervention would be cost-effective at a cost-effectiveness threshold of €80,000.[180] The NICE methods guideline[132] manual notes that, in general, interventions with an ICER of < £20,000 per QALY gained are considered to be cost-effective. ICER values of > £30,000 per QALY gained require consideration of the certainty of the ICER and evidence that the assessment of the change in the health-related quality of life is inadequately captured and that the intervention adds demonstrable and distinct substantial benefits that may not have been adequately captured in the measurement of health gain.

In the present study, the ICER for the base-case analysis is 55-fold higher than the accepted cost-effectiveness threshold of £30,000. There was a low probability of cost-effectiveness (< 1%) up to a threshold of £200,000 per QALY gained. Subgroup analyses covering cause of cardiac arrest, age, sex, ambulance response time, time to drug administration, initial rhythm, witness status and bystander CPR did not identify any specific subgroups for which the ICER substantially improved. Sensitivity analyses that included societal costs, QALYs based on mRS values, a 12-month time horizon, a 12-month time

horizon and societal perspective, and a 12-month time horizon and QALYs based on mRS showed that the average INMB value is always < £0.

Furthermore, our separate decision-analytic model demonstrated that the survival benefits associated with adrenaline generate additional QALY benefits, and therefore improved cost-effectiveness, over an extended time horizon. Nevertheless, even over a lifetime time horizon, the mean ICER associated with adrenaline exceeds cost-effectiveness thresholds widely accepted by decision-makers and health technology assessment agencies. Alternative extrapolations of cost-effectiveness, beyond the parameters of the PARAMEDIC2 trial, that focus solely on individuals experiencing OHCA are unlikely to alter decisions to recommend adrenaline on cost-effectiveness grounds.

It is possible that some benefits of admission to intensive care following cardiac arrest were incompletely captured through focusing on survival and health-related quality-of-life outcomes. The prevalence of post-traumatic stress among relatives of patients who die from cardiac arrest is high.[181,182] It is possible that admission to hospital allows the family time to say goodbye and to be present at the time of death.[183] Whether or not this has a beneficial effect, and any economic gains therein, remains to be determined. Approximately 10% of patients who die in ICU following OHCA become solid organ donors.[184] This may yield additional economic and health-related quality-of-life gains to the organ recipient and is worthy of further evaluation.

Ethics considerations

The design and conduct of this trial required particularly careful ethics consideration, given the life-threatening and emergency nature of OHCA. The lack of conclusive evidence of benefit, uncertainty about potential harm from adrenaline, and the presence of clinical equipoise provided the ethics justification of the need for a placebo-controlled trial. The implementation of the trial generated public debate on the ethics implications of conducting research in emergency situations without prior consent from participants or their legal representative. The public information strategy and process for enabling people to register their wish not to participate that we developed is, so far as we are aware, the first such initiative in the UK.

The implications of the trial findings for patients, clinicians, policy-makers and commissioners of health care also require careful ethics consideration. How an individual balances the chance of survival with the chance of having severe neurological impairment will be shaped by their personal values, but in the moment of a cardiac arrest, it is not possible to take into account these values when making a treatment decision. Thus, the decision about whether or not adrenaline is given will be directed by a policy or guideline applicable to all patients, informed by available evidence. A further consideration for policy-makers and commissioners of health care is the overall cost and cost-effectiveness of any treatment. The NHS is a publicly funded health service with limited financial resources and an obligation to distribute these resources fairly for everyone in response to health-care need. Our health economic analysis suggests that adrenaline treatment would not meet the current NICE criteria for cost-effectiveness. Developing a policy recommendation for the use of adrenaline for OHCA requires a complex balancing of current clinical practice norms, empirical evidence, and values. Understanding the range of population perspectives regarding this decision will be an important element of developing such a policy.

Interpretation by the International Liaison Committee on Resuscitation

The ILCOR is a collaboration of resuscitation councils from around the world that collaborate to 'save more lives globally through resuscitation',[185] through the use of transparent evaluation of scientific data to promote, disseminate, and implement international consensus guidelines for resuscitation and first aid. The publication of the PARAMEDIC2 trial prompted the ILCOR to prioritise a review of vasopressors as treatment for cardiac arrest.[186] The ILCOR commissioned a systematic review and meta-analysis focusing on the use of standard-dose adrenaline (1 mg), compared with placebo, vasopressin, or adrenaline and vasopressin.[187] Similar to our Cochrane review,[55] the review found moderate-quality evidence that adrenaline improves the rate of ROSC, survival to hospital discharge

and 3-month survival among those experiencing OHCA. Subgroup analyses found that the improvement in short-term outcomes was more pronounced for non-shockable rhythms. The systematic review authors noted, in the pooled analysis, no improvement in mid-term (hospital discharge) neurological outcomes, but interpret it as showing a signal towards improved outcomes for 3-month survival, based on the findings from the PARAMEDIC2 trial [2.1% (82/3986) in the adrenaline group, compared with 1.6% (63/3979) in the placebo group; RR 1.30, 95% CI 0.94 to 1.80; absolute risk difference: 5 more per 1000 people, 95% CI 1 fewer to 13 more]. The authors acknowledge the loss to follow-up and very low event rates, leading to very low confidence in the effect estimate.

The ILCOR Advanced Life Support Task Force assessed the findings from the systematic review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision Framework.[188] The Task Force comprised 19 health-care professionals from around the world. No patient or public representatives participated in the Evidence to Decision Famework or in the development of treatment recommendations. The assessors considered the problem of OHCA as high priority. After considering the effect of adrenaline on ROSC, survival and neurological outcomes, the assessors judged the desirable effects of using adrenaline as moderate and judged the undesirable effects as small. The overall certainty of evidence was assessed to be moderate, noting that certainty varies according to outcome (high for ROSC, low for neurological outcomes). The ILCOR assessed that there was possibly important uncertainty or variability in how much people value the main outcomes, noting that the Core Outcome Set for Cardiac Arrest investigators reported that patients valued survival with favourable neurological outcome most highly.[165] The ILCOR's overall judgement of the balance between desirable and undesirable effects probably favours using adrenaline. They reported that the intervention was probably acceptable to key stakeholders and considered it feasible to implement, noting that, although there was no research identified about patient acceptability, adrenaline use is currently the standard of care in many settings.

The writing group concluded by recommending that adrenaline should be administered as soon as possible during CPR (strong recommendation for non-shockable rhythms, weak recommendation for shockable rhythms).[186]

Internal validity and methodological limitations

The internal validity of the trial is strengthened by the randomised, blinded, placebo-controlled design. Selection bias was minimised by the computer-generated randomisation sequence using the stratification method with concealed assignment, using ambulance service as a strata, with an allocation ratio of 1 : 1. This resulted in almost identical baseline characteristics of the key variables associated with outcome (age, sex, initial rhythm, cause of cardiac arrest, witnessed status, bystander CPR, ambulance response time and time to administration of the study intervention). Performance bias was reduced through the use of treatment packs that were identical in appearance. Laboratory testing of the trial IMP showed no changes in appearance throughout the duration of the trial. Trial participants were unconscious at the time of enrolment. No requests for unblinding were received during the treatment phase of the trial. Although not formally tested for, it is possible that some of the effects of adrenaline (e.g. rhythm transitions,[189,190] higher rate of ROSC, greater cardiovascular instability after ROSC[67,70,190]) may have led to paramedics forming a view on the composition of the trial drug. As the acute effects of adrenaline are short lived, it is less likely to have influenced those treating the patient in hospital. Detection bias was minimised by the use of outcome assessors who were not involved in the initial treatment of the participant. Many outcomes (e.g. ROSC, survival status) are objective and would not be influenced by knowledge of treatment allocation. No unblinding of participants or legal representatives occurred before outcome assessments were complete. The trial had very high rates of follow-up for survival up to 12 months after enrolment in the trial. By contrast, beyond hospital discharge, loss to follow-up for neurological outcomes and health-related quality of life increased significantly. Consistent with previous studies,[102,136,191] those with worse neurological outcomes were more likely to be LTFU. The trial was

registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry and outcomes were defined prior to the enrolment of the first patient. The trial protocol was finalised and approved prior to commencement of randomisation. This report contains all the trial outcomes, thus eliminating selective reporting as a source of bias.

External validity and generalisability

External validity is a question of whether or not the results of a study can be applied to patients other than those enrolled in the study.[192] External validity is a matter of judgement and depends on the characteristics of the participants included in the trial, the trial setting, the treatment regimens tested and the outcomes assessed.[193]

The PARAMEDIC2 trial was a pragmatic trial design, intended to show the real-world effectiveness of the intervention, and maximising the generalisability of findings.[194] Patient eligibility for inclusion was broad, with no exclusion based on age (other than < 16 years), sex, comorbidity (other than pregnancy), cause of arrest (other than anaphylaxis/asthma), location of arrest, witnessed status of arrest or initial cardiac arrest rhythm. The patients included in the trial were 'representative' of all OHCA patients attended by the respective ambulance services and where ALS is initiated. Similarly, all standard ALS interventions were provided to the trial participants, including chest compression, defibrillation and advanced airway management, as required, with the exception that standard adrenaline was substituted with trial drug drawn from a single trial treatment pack. The primary outcome of 'survival to 30 days post cardiac arrest' was an objective measurement, directly relevant to participants.

Ambulance system configuration is similar throughout the NHS and is based on a single-tier response system led by paramedics. Community first responders support emergency response systems. Physician involvement in initial phases of out-of-hospital resuscitation is relatively rare. NHS paramedics operate according to national clinical guidelines for cardiac arrest produced by the JRCALC.[87] These guidelines and those used in hospital for post-resuscitation care are based on the NICE-accredited Resuscitation Council (UK) guidelines,[86] which are consistent with the European Resuscitation Council guidelines.[88] Although resuscitation guidelines around the world are broadly similar and based on recommendations from the ILCOR, emergency system response configurations vary. In many parts of the USA, the paramedic-based system is supplemented by basic life support response units, meaning that there are often more emergency care workers at the scene of a cardiac arrest than in the UK. In urbanised areas, emergency response times are quicker, although there is wide variation.

Analysis of the national OHCA registry[103] and PARAMEDIC trial[102,136] databases for patients treated for OCHA revealed similar patient characteristics and outcomes to those reported in PARAMEDIC2.[39] An evaluation of adrenaline use in the London Ambulance Service prior to the trial (2012–13) showed similar findings.[195] Outside the UK, compared with the Norwegian i.v. versus no i.v. trial,[57] patients enrolled in PARAMEDIC2 were, on average, 4 years older (69 vs. 65 years) and were less likely to have a bystander-witnessed cardiac arrest (50% vs. 65%) or to have an initial shockable rhythm (19% vs. 33%). Compared with the PACA trial,[56] patients enrolled in the PARAMEDIC2 trial were also, on average, 4 years older and were as likely to have a bystander-witnessed arrest, but were less likely to have an initially shockable rhythm (45% in the PACA trial[56]). Observational data from the US Resuscitation Outcome Consortium for 13,053 patients from 264 EMS agencies across 11 geographically distinct sites, who sustained an OHCA and were treated with adrenaline between 2005–7, similarly showed a younger cohort of patients (mean age 65 years); the rate of bystander-witnessed cardiac arrest was lower (39%) than that seen in the PARAMEDIC2 trial, but the proportion of patients with an initially shockable rhythm was higher (23%).[38] A similar pattern is seen in data from Seattle for cardiac arrests (from 2006 to 2012).[196]

Some studies suggest that the timing of drug administration is critical to its effectiveness.[60,197–199] Adrenaline is recommended in European guidelines after the third attempt at defibrillation for shockable rhythms and after initiating ALS (CPR and airway management) for non-shockable rhythms. With OHCA, drug administration is usually delayed while paramedics travel to the scene of collapse, initiate CPR and defibrillation (when indicated) and obtain vascular access. In an evaluation of repeated doses of adrenaline conducted by the London Ambulance Service, the average time to the first dose of adrenaline was 21–26 minutes.[195] The time from collapse to drug treatment in the PARAMEDIC2 trial was, on average, 21 minutes. This is longer than the interval during in-hospital cardiac arrest (average 3 minutes)[197,200] and in the majority of animal cardiac arrest models (average 9.5 minutes).[201] The timing is, however, similar to a systematic review of time to drug administration across 17 studies (19.4 minutes, 95% CI 12.8 to 25.9 minutes),[202] and in more recent studies (range 13–24 minutes).[199,203–205] A subgroup analysis of time to drug administration and paramedic-witnessed cardiac arrest (in which case, adrenaline is likely to be given earlier) did not find evidence of an interaction. The practicalities of delivering early drug administration and its influence on outcomes remains to be determined.

Post-resuscitation care across acute NHS hospitals is informed by the NICE-accredited Resuscitation Council (UK) guidelines.[206] These guidelines follow the ILCOR and European Resuscitation Council/ European Society of Intensive Care Medicine recommendations.[91] Key components of these guidelines are the use of targeted temperature management, maintenance of physiological targets (arterial blood oxygen saturations of 94–98%, normocarbia, normoglycaemia, systolic blood pressure of > 100 mmHg), targeted temperature management, early percutaneous coronary intervention and delaying multimodal neuroprognostication to at least 72 hours after cardiac arrest. Although not formally protocolised or evaluated in the PARAMEDIC2 trial, an observational study across 286 NHS ICUs (29,621 OHCAs) suggested up to 60% use of targeted temperature management and a median time to treatment withdrawal of 5 days.[184] Evaluation of the Myocardial Ischaemia National Audit Project database through to 2016 showed percutaneous coronary intervention use in ST elevation myocardial infarction to be in the region of 75%, and 15% for non-ST elevation myocardial infarction.[207] Future data with the Intensive Care National Audit Project and HES may provide more granular insights into the post-resuscitation care of patients enrolled in the PARAMEDIC2 trial.

Chapter 7 Conclusions

Implications for health care

Cardiac arrest remains a common and important condition. The PARAMEDIC2 trial found that adrenaline is effective at restarting the heart, leading to a 3.6-fold higher proportion of patients being admitted to hospital than if adrenaline was not given. The effect on survival to 30 days was more modest: 1.5-fold higher, corresponding to a 0.8% absolute increase in survival, giving a number needed to treat to save one life of 112. Survival with a favourable neurological outcome did not significantly differ between the adrenaline and placebo groups from hospital discharge. This pattern of better survival but no significant improvement in neurological outcomes continued through to the 6-month follow-up. Health-related quality of life was significantly impaired among survivors of OHCA and did not differ by treatment arm. The ICER for adrenaline was estimated at £1,675,976 per QALY gained. Based on current standards, this indicates that adrenaline is not a cost-effective intervention for the treatment of cardiac arrest. Consultation with the wider patient and public community will be important when considering the implications of the PARAMEDIC2 trial for clinical practice.

Recommendations for research

Unanswered questions about the use of vasopressors in OHCA remain. These include questions about timing, dosage, rate of administration, route of administration and concomitant therapies. Given the uncertainty about the effect of adrenaline on neurological outcomes, further research is required to better understand patients' preferences in relation to survival and neurological outcome after OHCA. Further research should explore how patients and the public interpret the findings from the trial, the priorities of patients and the public, and the implications for practice of the findings.

The NHS guidelines support the use of the intraosseous route for drug administration if initial attempts at i.v. access fail. In the PARAMEDIC2 trial, one-third of patients received delayed drug administration through the intraosseous route. It is possible that an intraosseous-first strategy may have enabled drug treatments to be delivered earlier. However, recent observational studies[63,208] raise doubt about the effectiveness of the intraosseous route for drug administration. Such studies are nevertheless limited by resuscitation time bias and other unmeasured confounders. The inclusion of a placebo arm in the PARAMEDIC2 trial should allow a less biased comparison of the i.v. and intraosseous route, which may guide the need for further research on the role of i.v. and intraosseous drug administration.

The evidence produced by the PARAMEDIC2 trial demonstrates that adrenaline is highly effective at restarting the heart and sustaining survival to hospital admission. Despite active treatments in intensive care, two-thirds of these patients will die prior to hospital discharge. The majority of these patients (65%) die from the devastating consequences of post-cardiac arrest brain injury. Of those who survive the initial cardiac arrest, the majority experience some neurocognitive functional impairment, ranging from mild cognitive problems to survival in a persistent vegetative state. There is very limited evidence about effective neuroprotective strategies beyond targeted temperature management. A key priority for future research is to identify effective treatment strategies to mitigate the effects of post-resuscitation brain injury. For those who survive but are left with significant functional impairment, further research in defining the optimal post-resuscitation rehabilitation care pathway would be beneficial.

Finally, the ethics and clinical implications of vasopressor use in OHCA and its effects on organ donation also need to be explored:

- What value do patients and the public place on survival, survival with a favourable neurological outcome and survival with an unfavourable neurological outcome?
- How do the communities served by NHS ambulance services interpret the findings from the PARAMEDIC2 trial and what are their views on the implications for practice?
- In the context of cardiac arrest, where do patients and their relatives prefer to die (home or hospital)?
- Does the effect of adrenaline differ according to the time of administration?
- Does the effect of adrenaline differ according to the dose delivered or the strategy for delivery (bolus vs. infusion)?
- Does the route of administration (i.v. or intraosseous) influence outcomes?
- What post-resuscitation interventions can improve survival with a favourable neurological outcome?
- What effect does the use of adrenaline have on the rate of organ donation?

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Health economics tables and figures

TABLE 26 Hospital resource use: HES data

Assessment period	Category	Adrenaline arm ($N = 1833$)[a] n[b]	Adrenaline arm ($N = 1833$)[a] Participants with complete data (n)	Adrenaline arm ($N = 1833$)[a] Mean (SE)	Placebo arm ($N = 1094$)[a] n[b]	Placebo arm ($N = 1094$)[a] Participants with complete data (n)	Placebo arm ($N = 1094$)[a] Mean (SE)	Adrenaline vs. placebo Mean difference (95% CI)	Adrenaline vs. placebo p-value
0–6 months after randomisation	Inpatient stay – initial admission								
	Inpatient ward (days)	670	670	6.63 (0.54)	317	317	7.84 (0.9)	−1.2 (−3.5 to 0.91)	0.264
	ICU (days)	506	505	5.75 (0.43)	234	233	6.29 (0.69)	−0.54 (−2.13 to 1.07)	0.518
	Inpatient stay, re-admissions								
	Inpatient ward (days)	56	56	18.55 (3.74)	37	36	16.69 (4.8)	1.86 (−9.84 to 13.71)	0.746
	ICU (days)	15	15	9.8 (3.48)	7	7	13.29 (3.79)	−3.49 (−12.96 to 6.31)	0.478
	Other hospitalisation episodes								
	Accident and emergency (visits)	1700	1700	1.05 (0.01)	1040	1040	1.04 (0.01)	0.01 (−0.02 to 0.03)	0.95
	Day case (visits)	15	15	5.93 (4.95)	16	16	1.06 (0.06)	4.87 (−0.12 to 15.8)	0.402
	Outpatient attendance (visits)	281	281	5.12 (0.43)	144	144	6.07 (0.66)	−0.95 (−2.58 to 0.68)	0.224
6–12 months after randomisation[c]	Inpatient stay – re-admissions								
	Inpatient ward (days)	26	23	5.87 (1.24)	16	11	9.36 (4.84)	−3.49 (−14.42 to 4.32)	0.494
	ICU (days)	6	5	5.8 (2.27)	2	1	1 (0)	4.8 (1 to 12)	0.79
	Other hospitalisation episodes								
	Accident and emergency (visits)	30	26	2.27 (0.28)	19	13	1.54 (0.28)	0.73 (−0.08 to 1.45)	0.084
	Day case (visits)	10	10	9.1 (7.99)	5	4	1 (0)	8.1 (0.11 to 26.05)	0.062
	Outpatient attendance (visits)	91	71	7.45 (1.48)	62	40	4.3 (0.64)	3.15 (0.31 to 6.74)	0.028

a N refers to number of trial participants with at least one record from the following HES data sets: admitted care, accident and emergency, critical care and outpatient care.
b n refers to number of trial participants with HES records for each category of hospital resource use variable.
c The 12-month costs for patients with < 12 months of complete HES data (adrenaline group, $n = 31$; placebo group, $n = 26$) were treated as missing observations.

Notes

TABLE 27 Hospitalisation costs: HES data

Assessment period	Category	Adrenaline arm ($N = 1833$)[a] n[b]	Adrenaline arm ($N = 1833$)[a] Number of participants with data	Adrenaline arm ($N = 1833$)[a] Mean (SE) costs (£)	Placebo arm ($N = 1094$)[a] n[b]	Placebo arm ($N = 1094$)[a] Number of participants with data	Placebo arm ($N = 1094$)[a] Mean (SE) costs (£)	Adrenaline vs. placebo Mean difference (95% CI) (£)	Adrenaline vs. placebo p-value
0–6 months after randomisation	Inpatient stay – initial admission								
	Admitted patient care	670	670	4655 (227)	317	316	5536 (410)	−881 (−1854 to 9)	0.06
	Critical care	506	505	10,162 (608)	234	233	11,338 (1203)	−1175 (−3900 to 1494)	0.406
	Inpatient stay, re-admissions								
	Admitted patient care	56	56	9906 (1168)	37	36	10,353 (1984)	−447 (−4856 to 3848)	0.904
	Critical care	15	15	13,450 (4493)	7	7	19,395 (4947)	−5945 (−17,765 to 6726)	0.368
	Other hospitalisation episodes								
	ED	1700	1700	233 (2)	1040	1040	234 (3)	−1 (−8 to 6)	0.684
	Day case	15	15	2405 (1841)	16	16	925 (288)	1480 (−814 to 5634)	0.652
	Outpatient care	281	280	605 (45)	144	144	741 (77)	−136 (−311 to 33)	0.14
	Total costs	1833	1831	5224 (295)	1094	1091	4777 (454)	448 (−718 to 1483)	0.412
0–12 months after randomisation[c]	Inpatient stay, re-admissions								
	Admitted patient care	736	692	4840 (266)	361	319	5855 (587)	−1015 (−2351 to 130)	0.11
	Critical care	525	492	9802 (602)	242	220	11,164 (1297)	−1362 (−4413 to 1248)	0.35
	Other hospitalisation episodes								
	ED	1706	1683	237 (3)	1041	1020	236 (3)	2 (−6 to 10)	0.762
	Day case	22	19	4062 (2891)	21	18	807 (258)	3255 (−194 to 9952)	0.124
	Outpatient care	284	253	790 (94)	145	119	757 (83)	34 (−198 to 291)	0.76
	Total costs	1833	1801	4913 (303)	1094	1066	4350 (468)	563 (−660 to 1644)	0.314

a N refers to number of trial participants with at least one record from the following HES data sets: admitted care, accident and emergency, critical care and outpatient care.
b n refers to number of trial participants with HES records for each category of hospital resource use variable.
c The 12-month costs for patients with < 12 months of complete HES data (adrenaline group, $n = 31$; placebo group, $n = 26$) were treated as missing observations.

Notes

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TABLE 28 Resources use for NHS and PSS by trial arm: CRF data, all patients

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
0–3 months after randomisation	Emergency response (minutes)						
	Time 1 (arrival at scene to departure) (minutes)	4013	60.279 (0.779)	3999	58.745 (0.548)	1.534 (–0.2 to 3.392)	0.1
	Time 2[a] (departure from scene to arrival at hospital or mortuary) (minutes)	4011	70.457 (0.234)	3992	70.04 (0.298)	0.418 (–0.332 to 1.151)	0.244
	Intervention dose						
	Number of syringes given	4008	4.923 (0.04)	3990	5.075 (0.037)	–0.152 (–0.266 to 0.052)	0.004
	Inpatient stay – initial admission (days)						
	ED	4006	0.51 (0.009)	3996	0.309 (0.008)	0.201 (0.179 to 0.224)	< 0.001
	General ward	4013	0.792 (0.098)	3998	0.496 (0.072)	0.296 (0.078 to 0.536)	0.008
	ICU	4013	0.91 (0.059)	3999	0.472 (0.047)	0.438 (0.298 to 0.592)	< 0.001
	Inpatient stay – repeat admissions (days)						
	ED	3974	0.005 (0.001)	3970	0.003 (0.001)	0.001 (–0.002 to 0.004)	0.652
	General ward	3973	0.048 (0.017)	3970	0.024 (0.011)	0.024 (–0.013 to 0.066)	0.214
	ICU						
	Outpatient attendance (visits)						
	Cardiology	3972	0.02 (0.004)	3968	0.016 (0.003)	0.005 (–0.005 to 0.014)	0.392
	Cardiac rehabilitation	3974	0.036 (0.009)	3969	0.033 (0.011)	0.003 (–0.025 to 0.029)	0.85
	Nursing/residential home	3974	0.062 (0.03)	3970	0.035 (0.02)	0.027 (–0.039 to 0.107)	0.422
	Other outpatient attendance	3974	0.029 (0.009)	3968	0.038 (0.018)	–0.009 (–0.051 to 0.027)	0.738

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Primary health-care contact (number of contacts)						
	District nurse	3976	0.025 (0.008)	3970	0.017 (0.006)	0.007 (−0.012 to 0.026)	0.466
	GP, surgery visit	3976	0.034 (0.005)	3970	0.029 (0.005)	0.005 (−0.011 to 0.019)	0.558
	GP, home visit	3976	0.003 (0.001)	3970	0.003 (0.001)	0 (−0.004 to 0.003)	0.834
	GP, telephone consultation	3976	0.002 (0.001)	3969	0.002 (0.001)	0 (−0.002 to 0.002)	0.668
	Practice nurse	3976	0.001 (0.001)	3969	0 (0)	0.001 (0 to 0.002)	0.916
	Physiotherapy	3976	0.037 (0.035)	3969	0 (0)	0.037 (0 to 0.111)	0.144
	Occupational therapy	3976	0.001 (0.001)	3969	0.001 (0.001)	0 (−0.001 to 0.001)	0.442
	Social worker	3976	0.003 (0.001)	3970	0.002 (0.001)	0.001 (−0.003 to 0.004)	0.854
	Speech therapy	3976	0.009 (0.006)	3970	0.012 (0.008)	−0.003 (−0.024 to 0.016)	0.772
	Psychiatrist	3976	0.001 (0.001)	3970	0.001 (0.001)	0 (−0.002 to 0.002)	0.646
	Psychology	3976	0.005 (0.004)	3970	0.006 (0.004)	−0.001 (−0.012 to 0.011)	0.786
	Counsellor	3976	0.001 (0.001)	3970	0.001 (0.001)	0.001 (−0.001 to 0.002)	0.982
	Home care worker	3976	0.107 (0.06)	3970	0.051 (0.038)	0.056 (−0.07 to 0.22)	0.4
	Lunch or social club	3976	0.003 (0.003)	3970	0.007 (0.004)	−0.003 (−0.013 to 0.006)	0.498
	Self-help groups	3976	0.046 (0.033)	3970	0.005 (0.003)	0.041 (−0.007 to 0.112)	0.274
	Meals and laundry	3976	0.046 (0.036)	3970	0.026 (0.016)	0.02 (−0.045 to 0.11)	0.716
	Other community care	3976	0 (0)	3969	0.002 (0.002)	−0.002 (−0.006 to 0.001)	0.184
	Medications						
	Medication, number of items	3975	2.119 (0.016)	3970	2.088 (0.012)	0.031 (−0.009 to 0.07)	0.132
	Aids and adaptations (per item/pair when appropriate)						
	Defibrillator	3974	0 (0)	3969	0 (0)	0 (−0.001 to 0)	< 0.001
	Heart monitor	3974	0.001 (0.001)	3969	0 (0)	0 (−0.001 to 0.001)	0.62
	PEG pump	3974	0 (0)	3969	0 (0)	0 (0 to 0.001)	0.432

continued

TABLE 28 Resources use for NHS and PSS by trial arm: CRF data, all patients (*continued*)

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Hoist	3974	0.001 (0.001)	3969	0 (0)	0.001 (0 to 0.001)	0.954
	Wheelchair	3974	0.001 (0.001)	3969	0 (0)	0.001 (0 to 0.002)	0.258
	Walking aid	3974	0.003 (0.001)	3969	0.003 (0.001)	0 (−0.003 to 0.002)	0.558
	Hand aid	3974	0 (0)	3969	0.001 (0.001)	−0.001 (−0.002 to 0)	0.022
	Stair rail	3974	0 (0)	3969	0 (0)	0 (0 to 0)	< 0.001
	Other aids and adaptations	3974	0.005 (0.002)	3969	0.003 (0.001)	0.003 (0 to 0.006)	0.158
3–6 months after randomisation	Inpatient stay (days)						
	ED	3965	0.005 (0.002)	3953	0.004 (0.001)	0.002 (−0.002 to 0.006)	0.62
	General ward	4004	0.114 (0.059)	3988	0.078 (0.043)	0.036 (−0.094 to 0.195)	0.638
	ICU	4006	0.008 (0.008)	3989	0 (0)	0.008 (0 to 0.025)	0.276
	Outpatient attendance (visits)						
	Cardiology	3964	0.017 (0.003)	3951	0.011 (0.003)	0.006 (−0.002 to 0.013)	0.172
	Cardiac rehabilitation	3964	0.036 (0.011)	3953	0.034 (0.012)	0.002 (−0.029 to 0.033)	0.97
	Nursing/residential home	3964	0.102 (0.047)	3952	0.028 (0.024)	0.074 (−0.019 to 0.182)	0.124
	Other outpatient attendance	3963	0.005 (0.002)	3953	0.005 (0.002)	−0.001 (−0.006 to 0.005)	0.784
	Primary health-care contact (number of contacts)						
	District nurse	3965	0.059 (0.038)	3954	0.004 (0.001)	0.055 (0.003 to 0.141)	0.004
	GP, surgery visit	3965	0.035 (0.007)	3954	0.022 (0.005)	0.013 (−0.003 to 0.029)	0.134
	GP, home visit	3965	0.005 (0.002)	3954	0.002 (0.001)	0.004 (−0.001 to 0.008)	0.154
	GP, telephone consultation	3964	0.001 (0.001)	3953	0.002 (0.001)	−0.001 (−0.003 to 0.002)	0.384
	Practice nurse	3964	0 (0)	3953	0 (0)	0 (0 to 0.001)	0.42
	Physiotherapy	3964	0.001 (0.001)	3953	0 (0)	0.001 (0 to 0.003)	0.772
	Occupational therapy	3964	0 (0)	3953	0.001 (0.001)	−0.001 (−0.002 to 0)	< 0.001

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Social worker	3965	0.005 (0.002)	3954	0.002 (0.001)	0.003 (–0.001 to 0.008)	0.276
	Speech therapy	3965	0.003 (0.002)	3954	0 (0)	0.002 (0 to 0.006)	0.238
	Psychiatrist	3965	0.001 (0.001)	3954	0 (0)	0 (–0.001 to 0.001)	0.606
	Psychology	3965	0.002 (0.001)	3954	0.002 (0.001)	0 (–0.002 to 0.003)	0.84
	Counsellor	3965	0.003 (0.003)	3954	0.001 (0.001)	0.002 (–0.002 to 0.008)	0.786
	Home care worker	3965	0.069 (0.05)	3954	0.002 (0.002)	0.067 (–0.003 to 0.181)	0.218
	Lunch or social club	3965	0.001 (0.001)	3954	0 (0)	0.001 (0 to 0.004)	0.762
	Self-help groups	3965	0.027 (0.024)	3954	0.004 (0.003)	0.023 (–0.006 to 0.084)	0.344
	Meals and laundry	3965	0.047 (0.033)	3954	0.001 (0.001)	0.046 (–0.001 to 0.116)	0.174
	Other community care	3964	0.007 (0.006)	3953	0 (0)	0.007 (0 to 0.024)	0.146
	Medications						
	Medication, number of items	3961	2.063 (0.012)	3952	2.03 (0.007)	0.033 (0.008 to 0.058)	0.006
	Aids and adaptations (per item/pair when appropriate)						
	Defibrillator	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	Heart monitor	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	PEG pump	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	Hoist	3964	0.001 (0.001)	3954	0 (0)	0.001 (0 to 0.002)	0.358
	Wheelchair	3964	0.002 (0.001)	3954	0.001 (0.001)	0.001 (–0.001 to 0.002)	0.68
	Walking aid	3964	0.001 (0.001)	3954	0.001 (0.001)	0.001 (–0.001 to 0.002)	0.954
	Hand aid	3964	0 (0)	3954	0 (0)	0 (–0.001 to 0)	< 0.001
	Stair rail	3964	0 (0)	3954	0 (0)	0 (–0.001 to 0)	< 0.001
	Other aids and adaptations	3964	0.005 (0.002)	3954	0.001 (0.001)	0.004 (0.001 to 0.007)	0.03

PEG, percutaneous endoscopic gastrostomy.

a We added 60 minutes (step-down or restock time) to account for time that ambulance crew use to restock before they are available for the next assignment. This is based on asking ambulance crew during one of the meetings to discuss the trial results.

TABLE 29 Resource use for non-NHS and PSS by trial arm: CRF data, all patients

		Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
0- to 3-month post-randomisation assessment period	Medications (item)						
	Medication, number of items	3975	2.001 (0.001)	3970	2 (0)	0.001 (0 to 0.001)	0.952
	Additional costs (number of occurrences)						
	Child care	3976	0.013 (0.002)	3970	0.008 (0.001)	0.005 (0.001 to 0.01)	0.048
	House work	3976	0.014 (0.002)	3970	0.01 (0.002)	0.004 (–0.001 to 0.009)	0.144
	Travel costs	3977	0.024 (0.004)	3970	0.015 (0.003)	0.01 (0 to 0.019)	0.052
	Other additional costs	3977	0.037 (0.005)	3970	0.024 (0.004)	0.014 (0 to 0.027)	0.062
3–6 months after randomisation	Medications (item)						
	Medication, number of items	3962	2 (0)	3953	2 (0)	0 (0 to 0.001)	0.456
	Additional costs (number of occurrences)						
	Child care	3964	0.008 (0.001)	3955	0.004 (0.001)	0.004 (0.001 to 0.007)	0.044
	House work	3964	0.009 (0.002)	3955	0.005 (0.001)	0.004 (0 to 0.008)	0.086
	Travel costs	3964	0.015 (0.003)	3955	0.008 (0.002)	0.007 (0.001 to 0.014)	0.036
	Other additional costs	3964	0.022 (0.004)	3955	0.011 (0.003)	0.011 (0.002 to 0.022)	0.024

TABLE 30 Resource use for NHS and PSS by trial arm: CRF data, survivors to hospital discharge

Assessment period	Category	Adrenaline arm (*N* = 128)		Placebo arm (*N* = 91)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
0–3 months after randomisation	Emergency response (minutes)						
	Time 1 (arrival at scene to departure)	128	44.388 (1.529)	91	40.24 (1.607)	4.148 (−0.245 to 8.459)	0.064
	Time 2[a] (departure from scene to arrival at hospital or mortuary)	128	74.017 (0.95)	91	73.859 (1.387)	0.158 (−3.18 to 3.237)	0.84
	Intervention dose						
	Number of syringes given	128	2.094 (0.144)	91	2.385 (0.224)	−0.291 (−0.825 to 0.223)	0.264
	Inpatient stay – initial admission (days)						
	ED	124	0.992 (0.014)	90	1.089 (0.058)	−0.097 (−0.227 to 0.003)	0.042
	General ward	127	22.118 (2.297)	90	19.233 (2.266)	2.885 (−3.624 to 8.857)	0.368
	ICU	127	10.283 (1.101)	91	8.143 (1.123)	2.141 (−0.911 to 5.027)	0.182
	Inpatient stay – repeat admissions (days)						
	ED	93	0.194 (0.05)	66	0.197 (0.058)	−0.003 (−0.16 to 0.15)	0.99
	General ward	92	2.065 (0.692)	66	1.455 (0.656)	0.611 (−1.258 to 2.511)	0.546
	ICU						
	Outpatient attendance (visits)						
	Cardiology	91	0.879 (0.132)	64	0.969 (0.169)	−0.09 (−0.526 to 0.331)	0.666
	Cardiac rehabilitation	93	1.527 (0.349)	65	2.015 (0.627)	−0.489 (−2.08 to 0.731)	0.502
	Nursing/residential home	93	2.634 (1.273)	66	2.106 (1.213)	0.528 (−2.754 to 3.844)	0.73
	Other outpatient attendance	93	1.237 (0.374)	64	2.359 (1.068)	−1.123 (−3.328 to 0.83)	0.304

continued

TABLE 30 Resource use for NHS and PSS by trial arm: CRF data, survivors to hospital discharge (*continued*)

Assessment period	Category	Adrenaline arm (*N* = 128)		Placebo arm (*N* = 91)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Primary health-care contact (number of contacts)						
	District nurse	95	1.032 (0.299)	66	1.045 (0.352)	−0.014 (−0.926 to 0.884)	0.992
	GP, surgery visit	95	1.411 (0.182)	66	1.727 (0.241)	−0.317 (−0.943 to 0.287)	0.31
	GP, home visit	95	0.116 (0.036)	66	0.167 (0.088)	−0.051 (−0.263 to 0.108)	0.644
	GP, telephone consultation	95	0.084 (0.033)	65	0.123 (0.051)	−0.039 (−0.165 to 0.077)	0.544
	Practice nurse	95	0.021 (0.022)	65	0 (0)	0.021 (0 to 0.078)	0.76
	Physiotherapy	95	1.568 (1.596)	65	0 (0)	1.568 (0.01 to 5.117)	0.042
	Occupational therapy	95	0.021 (0.015)	65	0.031 (0.031)	−0.01 (−0.085 to 0.049)	0.852
	Social worker	95	0.126 (0.043)	66	0.136 (0.078)	−0.01 (−0.192 to 0.149)	0.986
	Speech therapy	95	0.389 (0.221)	66	0.742 (0.463)	−0.353 (−1.485 to 0.518)	0.548
	Psychiatrist	95	0.053 (0.028)	66	0.076 (0.047)	−0.023 (−0.136 to 0.08)	0.724
	Psychology	95	0.221 (0.159)	66	0.364 (0.236)	−0.143 (−0.709 to 0.368)	0.628
	Counsellor	95	0.042 (0.025)	66	0.03 (0.032)	0.012 (−0.073 to 0.087)	0.738
	Home care worker	95	4.495 (2.346)	66	3.076 (2.291)	1.419 (−5.2 to 7.616)	0.676
	Lunch or social club	95	0.137 (0.114)	66	0.394 (0.271)	−0.257 (−0.884 to 0.261)	0.408
	Self-help groups	95	1.916 (1.321)	66	0.273 (0.201)	1.643 (−0.426 to 4.5)	0.27
	Meals and laundry	95	1.926 (1.609)	66	1.576 (0.938)	0.351 (−2.92 to 4.276)	0.916
	Other community care	95	0.011 (0.011)	65	0.123 (0.129)	−0.113 (−0.414 to 0.029)	0.474
	Medications						
	Medication, number of items	94	7.043 (0.414)	66	7.318 (0.401)	−0.276 (−1.36 to 0.881)	0.596

Assessment period	Category	Adrenaline arm (*N* = 128)		Placebo arm (*N* = 91)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Aids and adaptations (per item/pair when appropriate)						
	Defibrillator	93	0 (0)	65	0.015 (0.015)	−0.015 (−0.05 to 0)	< 0.001
	Heart monitor	93	0.022 (0.015)	65	0.015 (0.015)	0.006 (−0.037 to 0.047)	0.794
	PEG pump	93	0.011 (0.01)	65	0 (0)	0.011 (0 to 0.034)	0.758
	Hoist	93	0.022 (0.015)	65	0 (0)	0.022 (0 to 0.052)	0.306
	Wheelchair	93	0.043 (0.022)	65	0 (0)	0.043 (0 to 0.09)	0.052
	Walking aid	93	0.118 (0.033)	65	0.185 (0.057)	−0.066 (−0.208 to 0.057)	0.296
	Hand aid	93	0.011 (0.011)	65	0.062 (0.03)	−0.051 (−0.118 to 0.005)	0.066
	Stair rail	93	0 (0)	65	0 (0)	0 (0 to 0)	< 0.001
	Other aids and adaptations	93	0.226 (0.056)	65	0.154 (0.045)	0.072 (−0.067 to 0.211)	0.292
3–6 months after randomisation	Inpatient stay (days)						
	ED, visits	84	0.25 (0.072)	49	0.306 (0.097)	−0.056 (−0.298 to 0.154)	0.616
	General ward	122	3.746 (1.826)	83	3.741 (2.092)	0.005 (−5.431 to 5.353)	0.98
	ICU	124	0.274 (0.263)	84	0 (0)	0.274 (0 to 0.992)	0.094
	Outpatient attendance (visits)						
	Cardiology	83	0.807 (0.106)	47	0.936 (0.219)	−0.129 (−0.617 to 0.295)	0.596
	Cardiac rehabilitation	83	1.711 (0.485)	49	2.755 (0.925)	−1.044 (−3.262 to 0.755)	0.298
	Nursing/residential home	83	4.867 (2.177)	48	2.271 (1.905)	2.597 (−3.022 to 8.345)	0.344
	Other outpatient attendance	82	0.232 (0.085)	49	0.429 (0.18)	−0.197 (−0.637 to 0.154)	0.328

continued

TABLE 30 Resource use for NHS and PSS by trial arm: CRF data, survivors to hospital discharge (*continued*)

Assessment period	Category	Adrenaline arm ($N = 128$)		Placebo arm ($N = 91$)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Primary health-care contact (number of contacts)						
	District nurse	84	2.774 (1.745)	50	0.28 (0.091)	2.494 (0.013 to 6.315)	0.046
	GP, surgery visit	84	1.631 (0.252)	50	1.72 (0.293)	−0.089 (−0.934 to 0.643)	0.826
	GP, home visit	84	0.25 (0.095)	50	0.12 (0.052)	0.13 (−0.072 to 0.342)	0.254
	GP, telephone consultation	83	0.06 (0.03)	49	0.143 (0.079)	−0.083 (−0.264 to 0.059)	0.348
	Practice nurse	83	0.012 (0.012)	49	0 (0)	0.012 (0 to 0.039)	0.714
	Physiotherapy	83	0.048 (0.049)	49	0 (0)	0.048 (0 to 0.16)	0.71
	Occupational therapy	83	0 (0)	49	0.061 (0.058)	−0.061 (−0.18 to 0)	< 0.001
	Social worker	84	0.214 (0.096)	50	0.14 (0.064)	0.074 (−0.143 to 0.298)	0.512
	Speech therapy	84	0.119 (0.075)	50	0.02 (0.02)	0.099 (−0.022 to 0.272)	0.136
	Psychiatrist	84	0.024 (0.017)	50	0.02 (0.019)	0.004 (−0.048 to 0.053)	0.902
	Psychology	84	0.083 (0.049)	50	0.12 (0.074)	−0.037 (−0.212 to 0.128)	0.7
	Counsellor	84	0.119 (0.118)	50	0.06 (0.046)	0.059 (−0.13 to 0.345)	0.794
	Home care worker	84	3.262 (2.398)	50	0.16 (0.127)	3.102 (−0.208 to 8.501)	0.196
	Lunch or social club	84	0.048 (0.047)	50	0 (0)	0.048 (0 to 0.158)	0.708
	Self-help groups	84	1.274 (1.111)	50	0.32 (0.286)	0.954 (−0.704 to 3.612)	0.454
	Meals and laundry	84	2.214 (1.531)	50	0.1 (0.064)	2.114 (−0.1 to 5.762)	0.168
	Other community care	83	0.337 (0.299)	49	0 (0)	0.337 (0 to 1.043)	0.084
	Medications						
	Medication, number of items	80	5.138 (0.435)	48	4.479 (0.4)	0.658 (−0.549 to 1.807)	0.272

Assessment period	Category	Adrenaline arm (*N* = 128)		Placebo arm (*N* = 91)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
	Aids and adaptations (per item/pair when appropriate)						
	Defibrillator	83	0 (0)	50	0 (0)	0 (0 to 0)	< 0.001
	Heart monitor	83	0 (0)	50	0 (0)	0 (0 to 0)	< 0.001
	PEG pump	83	0 (0)	50	0 (0)	0 (0 to 0)	< 0.001
	Hoist	83	0.06 (0.025)	50	0.02 (0.02)	0.04 (–0.021 to 0.105)	0.228
	Wheelchair	83	0.072 (0.029)	50	0.06 (0.034)	0.012 (–0.079 to 0.093)	0.842
	Walking aid	83	0.06 (0.032)	50	0.06 (0.034)	0 (–0.097 to 0.092)	0.974
	Hand aid	83	0 (0)	50	0.02 (0.02)	–0.02 (–0.071 to 0)	< 0.001
	Stair rail	83	0 (0)	50	0.02 (0.02)	–0.02 (–0.066 to 0)	< 0.001
	Other aids and adaptations	83	0.241 (0.072)	50	0.1 (0.057)	0.141 (–0.028 to 0.323)	0.112

PEG, percutaneous endoscopic gastrostomy.

a We added 60 minutes (step-down or restock time) to account for time that ambulance crew use to restock before they are available for the next assignment. This is based on asking ambulance crew during one of the meetings to discuss the trial results.

TABLE 31 Resources use for non-NHS and PSS by trial arm: CRF data, survivors to hospital discharge

Assessment period	Category	Adrenaline arm (*N* = 128)		Placebo arm (*N* = 128)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean (SE)	Participants with complete data (*n*)	Mean (SE)	Mean difference (bootstrapped 95% CI)	*p*-value
0- to 3-month post-randomisation assessment period	Medications						
	Medication, number of items	94	2.021 (0.015)	66	2 (0)	0.021 (0 to 0.054)	0.274
	Additional costs (number of occurrences)						
	Child care	95	0.558 (0.051)	66	0.5 (0.062)	0.058 (−0.102 to 0.208)	0.512
	House work	95	0.579 (0.054)	66	0.576 (0.082)	0.003 (−0.195 to 0.178)	0.994
	Travel costs	96	1.01 (0.099)	66	0.894 (0.128)	0.116 (−0.22 to 0.422)	0.514
	Other additional costs	96	1.552 (0.15)	66	1.424 (0.202)	0.128 (−0.381 to 0.585)	0.596
3–6 months after randomisation	Medications						
	Medication, number of items	81	2.012 (0.013)	49	2 (0)	0.012 (0 to 0.042)	0.726
	Additional costs (number of occurrences)						
	Child care	83	0.361 (0.053)	51	0.294 (0.069)	0.067 (−0.117 to 0.242)	0.472
	House work	83	0.41 (0.062)	51	0.353 (0.082)	0.057 (−0.157 to 0.272)	0.64
	Travel costs	83	0.735 (0.103)	51	0.627 (0.123)	0.107 (−0.224 to 0.433)	0.582
	Other additional costs	83	1.048 (0.154)	51	0.824 (0.2)	0.225 (−0.306 to 0.757)	0.44

TABLE 32 Unit costs for NHS, non-NHS and PSS

Type of resource	Unit cost (£)	Unit	Source	Notes
Emergency response				
Emergency ambulance	8.00	Minute	PSSRU 2008,[160] p. 82	£6.80 (2008) prices inflated to £8.00 (2017 prices)
Adrenaline injection	6.87	Syringe	BNF 2016/17[142]	1 mg/10 ml (1 in 10,000) dilute solution for injection pre-filled syringes (Martindale Pharmaceuticals Ltd, Wooburn Green, UK)
Primary source of unit cost of hospital services (raw resource use data derived from HES), mean (SD), range				
Inpatients (initial): £6022.47 (£20,869.58), £352–683,381		Inpatient spell	*National Schedule of Reference Costs, 2016–17*[135]	
Inpatients (re-admission): £3804.74 (£20,877.28), £211–41,151		Inpatient spell	*National Schedule of Reference Costs, 2016–17*[135]	
Critical care (initial): £11,289.47 (£19,539.52), £348–364,247		Inpatient spell	*National Schedule of Reference Costs, 2016–17*[135]	
Critical care (re-admissions): £13,817.98 (£18,635.79), £1202–64,739		Inpatient spell	*National Schedule of Reference Costs, 2016–17*[135]	
Accident and emergency: £233.79 (£93.93), £83–1045		Visit	*National Schedule of Reference Costs, 2016–17*[135]	
Outpatients (first appointment): £291.41 (£423.15), £32–1714		Attendance	*National Schedule of Reference Costs, 2016–17*[135]	
Outpatients (follow-up): £353.95 (£423.73), £32–5659		Attendance	*National Schedule of Reference Costs, 2016–17*[135]	
Secondary source of unit costs for hospital services (raw resource use data derived from trial CRFs) *Inpatient care*				
ED visit	389.81	Visit	*National Schedule of Reference Costs, 2016–17*[135]	Emergency medicine (service code T01A; currency code VB02ZZ)
ICU bed-day	2114.13	Bed-day	*National Schedule of Reference Costs, 2016–17*[135]	Average cost of 0–6 or more organs supported (CCU01 and XC01Z-XC07Z) weighted by activity
Cardiac ward bed-day	305.85	Bed-day	*National Schedule of Reference Costs, 2016–17*[135]	Non-elective inpatients; excess bed-days
Secondary (outpatient services)				
Cardiology	137.07	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	Service code 320

continued

TABLE 32 Unit costs for NHS, non-NHS and PSS (*continued*)

Type of resource	Unit cost (£)	Unit	Source	Notes
Cardiac rehabilitation	79.70	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	Service code 327
Surgery	141.19	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	Service code 100
Neurology	171.98	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	Service code 400
Ophthalmology	95.15	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	Service code 130
Urology	111.61	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	Service code 101
Angiography	169.00	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	RD32Z contrast fluoroscopy procedures with duration of > 40 minutes
Echocardiography	74.00	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	RD51A
Haematology/oncology	176.24	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	370
Podiatry	45.81	Attendance	*National Schedule of Reference Costs, 2016–17*[135]	653
Nursing/residential home	162.00	Attendance	PSSRU 2017[140]	Local authority own-provision residential care for older people (£162/day, p. 35[140])
Home carers twice a day	27.00	Attendance	PSSRU 2017[140]	p. 178.[140] Face to face: £26 per hour on a weekday (£27 per hour on weekend day, £27 per hour on night-time weekday); assumed 1 hour of care provided each day at £27 per hour
Other outpatient services: mean £155.78 (SD £244.19), range £1–2114				
Community health and social care services				
Counsellor	53.00	Contact	PSSRU 2017[140]	Community-based professional (band 7) costing £53 per hour (pages 153–155); average length of surgery consultation (PSSRU 2013, page 54)

TABLE 32 Unit costs for NHS, non-NHS and PSS (*continued*)

Type of resource	Unit cost (£)	Unit	Source	Notes
District nurse	41.04	Contact	PSSRU 2013[209]	The mean average cost for a face-to-face contact in district nursing services for 2012/2013 was £39, inflated to 2017 prices
GP, home visit	38.00	Contact	PSSRU 2017[140]	Per patient contact lasting 9.22 minutes including CO_2 emissions (page 162)
GP, surgery visit	37.00	Contact	PSSRU 2017[140]	Per surgery consultation lasting 9.22 minutes (page 162)
GP, telephone consultation	28.49	Contact	PSSRU 2017[140]	Per telephone consultation lasting 7.1 minutes (PSSRU 2013, page 191)
Home care worker	13.50	Contact	PSSRU 2017[140]	Page 178. Face to face: £26 per hour weekday (£27 per day-time weekend, £27 per night-time weekday, £27 per night-time weekend). Assumed 30 minutes contact at £27 per hour
Meals and laundry	6.94	One meal	PSSRU 2014[210]	The average cost per meal on wheels was £6.60 for the local authority in 2012/13 (PSSRU Unit Costs 2014, page 127). Inflated to 2017 prices using the Hospital & Community Health Services (HCHS) Pay and Prices index
Occupational therapy	64.99	Contact	*National Schedule of Reference Costs, 2016–17*[135]	Occupational Therapy (service code 951)
Physiotherapy	48.00	Contact	*National Schedule of Reference Costs, 2016–17*[135]	Service code 650
Practice nurse	10.85	Contact	PSSRU 2017[140]	Practice nurse hourly costs including qualifications £42 (page 160); duration of contact 15.5 minutes (PSSRU 2013, page 188)
Psychiatrist	84.57	Contact	*National Schedule of Reference Costs, 2016–17*[135]	Liaison Psychiatry (service code 722)
Psychology	168.65	Contact	*National Schedule of Reference Costs, 2016–17*[135]	Clinical Psychology (service code 656)

continued

TABLE 32 Unit costs for NHS, non-NHS and PSS (*continued*)

Type of resource	Unit cost (£)	Unit	Source	Notes
Lunch or social club	6.94	One meal	PSSRU 2014[210]	The average cost per meal on wheels was £6.60 for the local authority in 2012/13 (PSSRU 2014, page 127). Inflated to 2017 prices using the Hospital & Community Health Services (HCHS) Pay and Prices index
Social worker	43.07	Contact	PSSRU 2017[140]	Social worker (adult services) with qualifications cost £59 per hour, page 174; assumed 73% of time is spent on client-related activities (PSSRU 2017, page 174) including direct contact (includes travel)
Speech therapy	96.52	Contact	*National Schedule of Reference Costs, 2016–17*[135]	Service code 652
Other primary care services: mean £58.98 (SD £19.43), range £21–98				
Additional costs[a] over 6 months for the adrenaline group, *n*; mean (SD), range	61; £3634 (£6590.44), £0.93–31,400			
Additional costs over 6 months for the adrenaline group, *n*; mean (SD), range	40; £2468 (£3805.61), £0.20–16,040			

PSSRU, Personal Social Services Research Unit.

a Additional non-health and social care costs reported by patients and or their proxies. These include child-care costs, purchase of equipment and over-the-counter medication by patients themselves, laundry, hospital parking charges and lost income.

TABLE 33 NHS and PSS costs (2017 prices) by trial arm, all patients, based on resource use collected through trial CRF data

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
0–3 months after randomisation	Emergency response costs						
	Time 1 (arrival at scene to departure)	4012	1152.27 (17.13)	3999	1099.38 (10.71)	52.89 (14.73 to 91.44)	0.002
	Time 2[a] (arrival at scene to departure)	4011	563.66 (1.87)	3992	560.32 (2.38)	3.34 (−2.66 to 9.21)	0.244
	Total emergency response costs	4010	1716.03 (17.05)	3992	1659.61 (10.41)	56.41 (18.54 to 94.42)	< 0.001
	Intervention costs						
	Syringes given	4008	33.82 (0.27)	3990	0 (0)	33.82 (33.27 to 34.32)	< 0.001
	Inpatient costs						
	ED	7980	99.26 (1.6)	7966	60.43 (1.52)	38.83 (34.66 to 43.08)	< 0.001
	General ward	7986	129.07 (15.65)	7968	79.88 (11.44)	49.19 (13.4 to 87.45)	0.006
	ICU	4013	1924.47 (124.11)	3999	997.59 (99.04)	926.88 (629.78 to 1250.56)	< 0.001
	Total inpatient costs	3964	2093.96 (128.43)	3967	1082.18 (88.63)	1011.78 (729.39 to 1325.13)	< 0.001
	Outpatient costs						
	Cardiology	3972	2.76 (0.5)	3968	2.14 (0.45)	0.62 (−0.64 to 1.91)	0.326
	Cardiac rehabilitation	3974	2.85 (0.68)	3969	2.63 (0.88)	0.22 (−2.03 to 2.31)	0.83
	Nursing/residential home	3974	9.99 (4.91)	3970	5.67 (3.24)	4.32 (−6.28 to 17.34)	0.412
	Other outpatient costs	3972	3.12 (1.14)	3964	2.63 (1.16)	0.49 (−2.59 to 3.6)	0.674
	Total outpatient costs	3967	18.62 (5.63)	3961	10.63 (3.38)	8 (−3.77 to 21.61)	0.196

continued

TABLE 33 NHS and PSS costs (2017 prices) by trial arm, all patients, based on resource use collected through trial CRF data (*continued*)

Assessment period	Category	Adrenaline arm ($N = 4015$)		Placebo arm ($N = 3999$)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
	Primary health-care costs						
	GP, surgery visit	3976	1.25 (0.2)	3970	1.06 (0.2)	0.18 (–0.39 to 0.7)	0.53
	GP, home visit	3976	0.11 (0.03)	3970	0.11 (0.05)	0 (–0.13 to 0.11)	0.98
	GP, telephone consultation	3976	0.06 (0.02)	3969	0.06 (0.02)	0 (–0.07 to 0.06)	0.936
	District nurse	3976	1.13 (0.33)	3970	0.71 (0.25)	0.41 (–0.39 to 1.24)	0.326
	Practice nurse	3976	0.01 (0.01)	3969	0 (0)	0.01 (0 to 0.02)	0.644
	Physiotherapy	3976	1.8 (1.7)	3969	0 (0)	1.8 (0.01 to 5.34)	0.034
	Occupational therapy	3976	0.03 (0.02)	3969	0.03 (0.03)	0 (–0.08 to 0.07)	0.898
	Social worker	3976	0.13 (0.05)	3970	0.1 (0.06)	0.03 (–0.13 to 0.17)	0.69
	Speech therapy	3976	0.9 (0.56)	3970	1.19 (0.76)	–0.29 (–2.28 to 1.55)	0.8
	Psychiatrist	3976	0.11 (0.06)	3970	0.11 (0.07)	0 (–0.17 to 0.15)	0.898
	Psychology	3976	0.89 (0.69)	3970	1.02 (0.71)	–0.13 (–2.03 to 1.87)	0.848
	Home care worker	3976	1.45 (0.82)	3970	0.69 (0.51)	0.76 (–0.95 to 2.97)	0.4
	Lunch or social club	3976	0.02 (0.02)	3970	0.05 (0.03)	–0.02 (–0.09 to 0.04)	0.448
	Self-help groups	3976	0 (0)	3970	0 (0)	0 (0 to 0)	< 0.001
	Meals and laundry	3976	0.32 (0.25)	3970	0.18 (0.11)	0.14 (–0.31 to 0.76)	0.72
	Counsellor	3976	0.05 (0.03)	3970	0.03 (0.03)	0.03 (–0.05 to 0.12)	0.606
	Other community care costs	3976	2.45 (2.31)	3969	0.09 (0.07)	2.35 (–0.13 to 7.2)	0.414
	Total community care costs	3976	10.69 (4.76)	3969	5.42 (1.67)	5.27 (–2.75 to 17.05)	0.308

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
	Medication costs						
	Medication	3975	6.8 (1.7)	3970	4.98 (1.68)	1.82 (−2.96 to 6.61)	0.45
	Aids and adaptations costs						
	Defibrillator	3974	0 (0)	3968	0 (0)	0 (0 to 0)	< 0.001
	Heart monitor	3974	0 (0)	3969	0 (0)	0 (0 to 0)	< 0.001
	PEG pump	3973	0 (0)	3969	0 (0)	0 (0 to 0)	< 0.001
	Hoist	3974	2.11 (1.46)	3969	0 (0)	2.11 (0 to 5.27)	0.262
	Wheelchair	3974	0.2 (0.1)	3969	0 (0)	0.2 (0.05 to 0.43)	0.038
	Walking aid	3974	0.1 (0.04)	3969	0.09 (0.04)	0.01 (−0.09 to 0.12)	0.882
	Hand aid	3974	0 (0)	3969	0 (0)	0 (0 to 0)	< 0.001
	Stair rail	3974	0 (0)	3969	0 (0)	0 (0 to 0)	< 0.001
	Other aids and adaptations costs	3968	0.49 (0.29)	3965	1.68 (1.29)	−1.19 (−4.25 to 0.69)	0.476
	Total aids and adaptations costs	3967	1.78 (1.29)	3964	1.75 (1.29)	0.02 (−3.8 to 3.88)	0.972
	0–3 months: total NHS and PSS costs	3937	3764.73 (127.92)	3936	2686.9 (90)	1077.83 (790.49 to 1406.45)	< 0.001

continued

TABLE 33 NHS and PSS costs (2017 prices) by trial arm, all patients, based on resource use collected through trial CRF data (*continued*)

Assessment period	Category	Adrenaline arm ($N = 4015$)		Placebo arm ($N = 3999$)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
3–6 months after randomisation	Inpatient costs						
	ED	3965	2.06 (0.65)	3953	1.48 (0.51)	0.59 (–0.83 to 2.23)	0.454
	General ward	4003	44.09 (15.06)	3987	36.02 (14.8)	8.07 (–36.25 to 50.39)	0.662
	ICU	4005	65.98 (51.66)	3989	15.37 (15.4)	50.61 (–29.07 to 182.2)	0.234
	Total inpatient costs	3961	83.1 (50.84)	3949	37.36 (19.5)	45.73 (–37.8 to 172.54)	0.388
	Outpatient costs						
	Cardiology	3964	2.32 (0.41)	3951	1.53 (0.4)	0.79 (–0.32 to 1.82)	0.136
	Cardiac rehabilitation	3964	2.86 (0.86)	3953	2.72 (0.95)	0.13 (–2.29 to 2.66)	0.948
	Nursing/residential home	3964	16.51 (7.68)	3952	4.47 (3.81)	12.04 (–3.12 to 29.51)	0.118
	Other outpatient costs	3963	0.6 (0.23)	3953	0.65 (0.31)	–0.05 (–0.85 to 0.67)	0.938
	Total outpatient costs	3960	18.59 (6.93)	3949	9.25 (4.02)	9.34 (–4.73 to 25.67)	0.218
	Primary health-care costs						
	GP, surgery visit	3965	1.29 (0.25)	3954	0.8 (0.18)	0.48 (–0.1 to 1.08)	0.116
	GP, home visit	3965	0.21 (0.08)	3954	0.06 (0.03)	0.15 (–0.01 to 0.34)	0.082
	GP, telephone consultation	3964	0.04 (0.02)	3953	0.05 (0.03)	–0.01 (–0.09 to 0.04)	0.646
	District nurse	3965	2.41 (1.57)	3954	0.15 (0.05)	2.27 (0.13 to 5.8)	0.002
	Practice nurse	3964	0 (0)	3953	0 (0)	0 (0 to 0.01)	0.494
	Physiotherapy	3964	0.05 (0.05)	3953	0 (0)	0.05 (0 to 0.15)	0.772
	Occupational therapy	3964	0 (0)	3953	0.05 (0.05)	–0.05 (–0.15 to 0)	< 0.001
	Social worker	3965	0.2 (0.09)	3954	0.08 (0.04)	0.12 (–0.04 to 0.35)	0.198

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
	Speech therapy	3965	0.24 (0.16)	3954	0.02 (0.02)	0.22 (0 to 0.58)	0.09
	Psychiatrist	3965	0.13 (0.09)	3954	0.02 (0.02)	0.11 (–0.04 to 0.3)	0.29
	Psychology	3965	0.3 (0.18)	3954	0.26 (0.16)	0.04 (–0.4 to 0.55)	0.95
	Home care worker	3965	0.93 (0.68)	3954	0.03 (0.02)	0.91 (–0.03 to 2.45)	0.206
	Lunch or social club	3965	0.01 (0.01)	3954	0 (0)	0.01 (0 to 0.03)	0.762
	Self-help groups	3965	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	Meals and laundry	3965	0.33 (0.23)	3954	0.01 (0.01)	0.32 (–0.01 to 0.81)	0.182
	Counsellor	3965	0.13 (0.14)	3954	0.04 (0.03)	0.09 (–0.09 to 0.41)	0.762
	Other community care costs	3964	0.28 (0.2)	3953	0 (0)	0.28 (0.03 to 0.78)	0.004
	Total community care costs	3964	6.54 (2.03)	3953	1.55 (0.33)	4.99 (1.36 to 9.26)	< 0.001
	Medications						
	Medication	3961	3.68 (1.2)	3952	1.03 (0.26)	2.65 (0.71 to 5.61)	0.002
	Aids and adaptations costs						
	Defibrillator	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	Heart monitor	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	PEG pump	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	Hoist	3964	5.28 (2.4)	3954	1.06 (1.04)	4.22 (–0.11 to 9.53)	0.106
	Wheelchair	3964	0.3 (0.12)	3954	0.15 (0.08)	0.15 (–0.1 to 0.45)	0.348
	Walking aid	3964	0.02 (0.02)	3954	0.02 (0.02)	0 (–0.05 to 0.05)	0.752
	Hand aid	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001
	Stair rail	3964	0 (0)	3954	0 (0)	0 (0 to 0)	< 0.001

continued

TABLE 33 NHS and PSS costs (2017 prices) by trial arm, all patients, based on resource use collected through trial CRF data (*continued*)

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
	Other aids and adaptations costs	3959	0.24 (0.2)	3954	0.01 (0.01)	0.22 (0 to 0.66)	0.15
	Total aids and adaptations costs	3959	4.78 (2.18)	3954	1.24 (1.09)	3.54 (−1 to 8.89)	0.12
	Total costs						
	3–6 months: total NHS and PSS costs	3948	93.75 (50.8)	3940	47.62 (20.86)	46.13 (−38.68 to 169.18)	0.382
	0–6 months: total NHS and PSS costs	3919	3641.84 (149.13)	3914	2548.36 (84)	1093.49 (800.43 to 1442)	< 0.001

PEG, percutaneous endoscopic gastrostomy.

a We added 60 minutes (step-down or restock time) to account for time that ambulance crew use to restock before they are available for the next assignment. This is based on asking ambulance crew during one of the meetings to discuss the trial results.

TABLE 34 Non-NHS and PSS costs by trial arm, all patients, CRF data

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
0–3 months after randomisation	Medications						
	Medication	3975	0.04 (0.03)	3970	0 (0)	0.04 (0 to 0.09)	0.26
	Additional costs						
	Child care	3976	0 (0)	3970	0 (0)	0 (0 to 0)	< 0.001
	Housework	3976	0.1 (0.09)	3970	0.24 (0.16)	−0.15 (−0.55 to 0.18)	0.364
	Travel costs	3977	1.66 (0.74)	3970	1.38 (0.63)	0.28 (−1.44 to 2.29)	0.73
	Other additional costs	3977	37.61 (10.35)	3970	18.3 (6.25)	19.31 (−4.21 to 42.52)	0.116
	Total additional costs	3976	39.19 (10.49)	3970	19.93 (6.45)	19.26 (−4.94 to 43.39)	0.124
	Total costs						
	0–3 months: total non-NHS and PSS costs	3973	37.34 (10.32)	3970	19.93 (6.45)	17.4 (−6.71 to 40.77)	0.156
	0–3 months: total societal costs	3936	3774.22 (127.5)	3936	2698.06 (91.12)	1076.16 (782.48 to 1403.42)	< 0.001

continued

TABLE 34 Non-NHS and PSS costs by trial arm, all patients, CRF data (*continued*)

Assessment period	Category	Adrenaline arm (*N* = 4015)		Placebo arm (*N* = 3999)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (95% CI) (£)	*p*-value
3–6 months after randomisation	Medications						
	Medication	3962	0 (0)	3953	0 (0)	0 (0 to 0)	< 0.001
	Additional costs						
	Child care	3964	0 (0)	3955	0.08 (0.08)	−0.08 (−0.23 to 0)	< 0.001
	Housework	3964	0.47 (0.32)	3955	0.07 (0.04)	0.39 (−0.06 to 1.1)	0.19
	Travel costs	3964	1.99 (1.02)	3955	0.4 (0.15)	1.59 (0 to 3.98)	0.052
	Other additional costs	3964	16.06 (7.56)	3955	4.47 (2.19)	11.59 (−0.73 to 30.2)	0.076
	Total additional costs	3964	18.52 (8.12)	3955	5.02 (2.25)	13.5 (0.43 to 33.45)	0.042
	Total costs						
	3–6 months: total on-NHS and PSS costs	3962	18.51 (8.13)	3953	4.95 (2.25)	13.56 (0.49 to 33.62)	0.038
	3–6 months: total societal costs	3948	110.4 (52.28)	3939	46.22 (20.39)	64.18 (−21.67 to 188.32)	0.192
	0–6 months: total non-NHS and PSS costs	3956	50.84 (14.62)	3952	15.07 (5.59)	35.77 (8.1 to 68.61)	0.01
	0–6 months: total societal costs	3919	3671.5 (150.28)	3913	2535.36 (82.89)	1136.14 (840.32 to 1484.33)	< 0.001

TABLE 35 NHS and PSS costs (2017 prices) by trial arm, survivors to hospital discharge, CRF data

Assessment period	Category	Adrenaline arm ($n = 128$)		Placebo arm ($n = 91$)		Adrenaline vs. placebo	
		Participants with complete data (n)	Mean cost (SE) (£)	Participants with complete data (n)	Mean cost (SE) (£)	Mean difference in costs (bootstrapped 95% CI) (£)	p-value
0–3 months after randomisation	Emergency response costs						
	Time 1 (arrival at scene to departure)	127	942.98 (43.08)	91	865 (50.55)	77.98 (–49.91 to 214.72)	0.23
	Time 2[a] (arrival at scene to departure)	128	592.13 (7.6)	91	590.87 (11.09)	1.26 (–25.44 to 25.9)	0.84
	Total emergency response costs	127	1535.32 (45.62)	91	1455.87 (53.8)	79.45 (–51.87 to 222.5)	0.242
	Intervention costs						
	Intervention costs	128	14.38 (0.99)	91	0 (0)	14.38 (12.44 to 16.33)	< 0.001
	Inpatient costs						
	ED	217	251.49 (9.81)	156	254.88 (11.24)	–3.39 (–35.3 to 24.12)	0.8
	General ward	219	4188.33 (433.9)	156	3581.97 (426.11)	606.36 (–597.29 to 1729.24)	0.322
	ICU	127	21,740.58 (2328.42)	91	17,215.06 (2373.78)	4525.52 (–1925.88 to 10,628.52)	0.182
	Total inpatient costs	88	29,425.72 (3032.74)	65	24,356.65 (3055.72)	5069.07 (–3985.61 to 13,777.15)	0.244
	Outpatient costs						
	Cardiology	91	120.5 (18.14)	64	132.79 (23.19)	–12.29 (–72.07 to 45.37)	0.67
	Cardiac rehabilitation	93	121.69 (27.84)	65	160.63 (49.99)	–38.93 (–165.76 to 58.3)	0.506
	Nursing/residential home	93	426.77 (206.19)	66	341.18 (196.55)	85.59 (–446.07 to 622.75)	0.73
	Other outpatient costs	91	136.08 (47.11)	60	173.61 (72.69)	–37.53 (–218.24 to 115.95)	0.676
	Total outpatient costs	86	859.01 (241.89)	57	738.4 (214.69)	120.61 (–494.23 to 763.48)	0.7

continued

TABLE 35 NHS and PSS costs (2017 prices) by trial arm, survivors to hospital discharge, CRF data (*continued*)

Assessment period	Category	Adrenaline arm (*n* = 128)		Placebo arm (*n* = 91)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (bootstrapped 95% CI) (£)	*p*-value
	Primary health-care costs						
	GP, surgery visit	95	52.19 (6.72)	66	63.91 (8.93)	−11.72 (−34.89 to 10.61)	0.312
	GP, home visit	95	4.4 (1.38)	66	6.33 (3.34)	−1.93 (−9.99 to 4.11)	0.644
	GP, telephone consultation	95	2.4 (0.93)	65	3.51 (1.44)	−1.11 (−4.69 to 2.19)	0.548
	District nurse	95	47.09 (12.98)	66	42.91 (14.46)	4.18 (−34.82 to 41.28)	0.826
	Practice nurse	95	0.23 (0.24)	65	0 (0)	0.23 (0 to 0.85)	0.76
	Physiotherapy	95	75.28 (76.62)	65	0 (0)	75.28 (0.47 to 245.62)	0.042
	Occupational therapy	95	1.37 (0.98)	65	2 (2)	−0.63 (−5.52 to 3.17)	0.858
	Social worker	95	5.44 (1.84)	66	5.87 (3.38)	−0.43 (−8.28 to 6.41)	0.98
	Speech therapy	95	37.59 (21.36)	66	71.66 (44.72)	−34.07 (−143.35 to 50.01)	0.548
	Psychiatrist	95	4.45 (2.39)	66	6.41 (3.96)	−1.96 (−11.47 to 6.74)	0.728
	Psychology	95	37.28 (26.86)	66	61.33 (39.74)	−24.05 (−119.63 to 62.08)	0.632
	Home care worker	95	60.68 (31.67)	66	41.52 (30.93)	19.16 (−70.19 to 102.83)	0.676
	Lunch or social club	95	0.95 (0.79)	66	2.84 (1.88)	−1.89 (−6.25 to 1.71)	0.376
	Self-help groups[b]	95	–	66	–	–	< 0.001
	Meals and laundry	95	13.37 (11.17)	66	10.94 (6.51)	2.43 (−20.26 to 29.67)	0.918
	Counsellor	95	2.23 (1.35)	66	1.61 (1.68)	0.63 (−3.86 to 4.63)	0.73
	Other community care costs	95	102.41 (103.78)	65	5.71 (4.21)	96.71 (−9.68 to 329.22)	0.542
	Total community care costs	95	447.36 (204.33)	65	330.81 (89.27)	116.55 (−250.21 to 580.86)	0.684

Assessment period	Category	Adrenaline arm ($n = 128$) Participants with complete data (n)	Adrenaline arm ($n = 128$) Mean cost (SE) (£)	Placebo arm ($n = 91$) Participants with complete data (n)	Placebo arm ($n = 91$) Mean cost (SE) (£)	Adrenaline vs. placebo Mean difference in costs (bootstrapped 95% CI) (£)	Adrenaline vs. placebo p-value
	Medications						
	Medication	94	287.66 (64.88)	66	299.49 (93.53)	−11.83 (−250.68 to 183.9)	0.97
	Aids and adaptations costs						
	Hoist	93	90.01 (61.56)	65	0 (0)	90.01 (0 to 215.81)	0.306
	Wheelchair	93	8.39 (4.31)	65	0 (0)	8.39 (0 to 17.53)	0.052
	Walking aid	93	4.36 (1.59)	65	5.41 (2.22)	−1.05 (−6.56 to 4.07)	0.726
	Hand aid	93	0.02 (0.02)	65	0.13 (0.07)	−0.11 (−0.25 to 0.01)	0.052
	Other aids and adaptations costs	87	22.24 (13.52)	61	109.1 (82.98)	−86.87 (−271.51 to 24.64)	0.336
	Total aids and adaptations costs	86	81.91 (63.42)	60	115.82 (84.33)	−33.91 (−263.39 to 159.46)	0.736
	Total costs						
	0–3 months: total NHS and PSS costs	72	32,669.22 (3589.54)	50	27,956.52 (3795.11)	4712.7 (−5527.48 to 14,967.31)	0.382
3–6 months after randomisation	Inpatient costs						
	ED	84	97.45 (27.96)	49	119.33 (37.73)	−21.88 (−116.02 to 60.14)	0.616
	General ward	121	1458.47 (450.89)	82	1,687.77 (697.84)	−229.3 (−1938.34 to 1295.45)	0.76
	ICU	123	2148.51 (1649.51)	84	0 (0)	2148.51 (17.47 to 5940.07)	0.032
	Total inpatient costs	80	4114.25 (2466.27)	45	1916.46 (957.58)	2197.79 (−2031.75 to 8385.56)	0.44

continued

TABLE 35 NHS and PSS costs (2017 prices) by trial arm, survivors to hospital discharge, CRF data (*continued*)

Assessment period	Category	Adrenaline arm ($n = 128$)		Placebo arm ($n = 91$)		Adrenaline vs. placebo	
		Participants with complete data (*n*)	Mean cost (SE) (£)	Participants with complete data (*n*)	Mean cost (SE) (£)	Mean difference in costs (bootstrapped 95% CI) (£)	*p*-value
	Outpatient costs						
	Cardiology	83	110.65 (14.53)	47	128.32 (30.04)	−17.67 (−84.6 to 40.45)	0.596
	Cardiac rehabilitation	83	136.35 (38.67)	49	219.58 (73.76)	−83.23 (−260.01 to 60.19)	0.298
	Nursing/residential home	83	788.53 (352.6)	48	367.88 (308.67)	420.66 (−489.54 to 1352)	0.344
	Other outpatient costs	82	29.24 (10.35)	49	52.8 (25.37)	−23.56 (−86.71 to 19.04)	0.384
	Total outpatient costs	79	932.02 (328.67)	45	812.04 (331.92)	119.97 (−835.56 to 1002.03)	0.736
	Primary health-care costs						
	GP, surgery visit	84	60.79 (9.33)	50	63.64 (10.85)	−2.85 (−34.14 to 24.32)	0.864
	GP, home visit	84	9.95 (3.62)	50	4.56 (1.99)	5.39 (−2.17 to 13.33)	0.19
	GP, telephone consultation	83	1.72 (0.86)	49	4.07 (2.25)	−2.35 (−7.51 to 1.67)	0.348
	District nurse	84	113.84 (71.63)	50	11.49 (3.73)	102.35 (0.54 to 259.15)	0.046
	Practice nurse	83	0.13 (0.13)	49	0 (0)	0.13 (0 to 0.42)	0.714
	Physiotherapy	83	2.31 (2.34)	49	0 (0)	2.31 (0 to 7.68)	0.71
	Occupational therapy	83	0 (0)	49	3.98 (3.77)	−3.98 (−11.7 to 0)	< 0.001
	Social worker	84	9.23 (4.12)	50	6.03 (2.77)	3.2 (−6.16 to 12.84)	0.51
	Speech therapy	84	11.49 (7.22)	50	1.93 (1.93)	9.56 (−2.09 to 26.22)	0.134
	Psychiatrist	84	6.04 (4.24)	50	1.69 (1.63)	4.35 (−2.54 to 14.61)	0.316
	Psychology	84	14.05 (8.31)	50	20.24 (12.44)	−6.18 (−35.83 to 21.53)	0.702
	Home care worker	84	44.04 (32.37)	50	2.16 (1.71)	41.88 (−2.81 to 114.76)	0.196
	Lunch or social club	84	0.33 (0.33)	50	0 (0)	0.33 (0 to 1.1)	0.708
	Self-help groups[b]	84	–	50	–	–	–

Assessment period	Category	Adrenaline arm ($n = 128$) Participants with complete data (n)	Adrenaline arm ($n = 128$) Mean cost (SE) (£)	Placebo arm ($n = 91$) Participants with complete data (n)	Placebo arm ($n = 91$) Mean cost (SE) (£)	Adrenaline vs. placebo Mean difference in costs (bootstrapped 95% CI) (£)	Adrenaline vs. placebo p-value
	Meals and laundry	84	15.37 (10.63)	50	0.69 (0.45)	14.67 (–0.69 to 39.99)	0.168
	Counsellor	84	6.31 (6.26)	50	3.18 (2.42)	3.13 (–6.87 to 18.28)	0.794
	Other community care costs	83	13.16 (9.54)	49	0 (0)	13.16 (1.47 to 36.46)	0.004
	Total community care costs	83	312.26 (86.32)	49	125.27 (19.78)	187 (29.94 to 378.04)	0.02
	Medications						
	Medication	80	182.04 (54.94)	48	84.86 (18.07)	97.18 (2.6 to 225.3)	0.044
	Aids and adaptations costs						
	Hoist	83	252.14 (105.74)	50	83.71 (83.57)	168.43 (–89.17 to 438.34)	0.222
	Wheelchair	83	14.1 (5.57)	50	11.7 (6.71)	2.4 (–15.49 to 18.19)	0.836
	Walking aid	83	0.97 (0.82)	50	1.45 (1.3)	–0.48 (–3.77 to 2.37)	0.768
	Hand aid	83	0 (0)	50	0.03 (0.03)	–0.03 (–0.12 to 0)	< 0.001
	Other aids and adaptations costs	78	12.07 (10.15)	50	1.07 (0.62)	11 (–0.77 to 34.02)	0.192
	Total aids and adaptations costs	78	242.69 (104.76)	50	97.99 (87.6)	144.7 (–117.87 to 409.13)	0.296
	Total costs						
	3–6 months: total NHS and PSS costs	67	5524.18 (2914.88)	36	3508.31 (1334.03)	2015.87 (–3297.29 to 8742.91)	0.598
	0–6 months: total NHS and PSS costs	54	33,385.85 (7293.82)	29	29,144.43 (4609.34)	4241.42 (–9982.79 to 22,538.49)	0.698

a We added 60 minutes (step-down or restock time) to account for the time that ambulance crew use to restock before they are available for the next assignment. This is based on asking ambulance crew during one of the meetings to discuss the trial results.

b The unit cost of running a self-help group activity for OHCA was not available, hence when calculating costs in the economic analysis, we assumed that the cost of self-help group activity is missing if a patient reported that they attended this activity.

TABLE 36 Non-NHS and PSS costs by trial arm, survivors to hospital discharge, CRF data

		Adrenaline arm ($n = 128$)		Placebo arm ($n = 91$)		Adrenaline vs. placebo	
Assessment period	Category	Participants with complete data (n)	Mean cost (SE) (£)	Participants with complete data (n)	Mean cost (SE) (£)	Mean difference in costs (bootstrapped 95% CI) (£)	p-value
0–3 months after randomisation	Medications						
	Medications (privately purchased)	94	1.64 (1.13)	66	0.14 (0.07)	1.5 (−0.14 to 4.01)	0.216
	Additional costs						
	Child care	95	0 (0)	66	0 (0)	0 (0 to 0)	< 0.001
	Housework	95	4 (3.55)	66	14.7 (9.18)	−10.7 (−33.51 to 4.85)	0.24
	Travel costs	96	68.8 (28.7)	66	83.18 (35.48)	−14.38 (−106.34 to 73.34)	0.762
	Other additional costs	96	1558.05 (405.25)	66	1100.98 (366.5)	457.06 (−640.29 to 1562.61)	0.404
	Total additional costs	95	1640.32 (411.74)	66	1198.86 (372.51)	441.46 (−667.47 to 1553.23)	0.416
	0–3 months: total non-NHS and PSS costs	92	1612.33 (420.67)	66	1199 (372.51)	413.33 (−686.8 to 1566.93)	0.444
3–6 months post randomisation assessment period	Medications						
	Medications (privately purchased)	81	0.07 (0.03)	49	0.12 (0.11)	−0.04 (−0.32 to 0.12)	0.818
	Additional costs						
	Child care	83	0 (0)	51	5.88 (5.69)	−5.88 (−18.37 to 0)	< 0.001
	Housework	83	22.29 (14.06)	51	5.67 (3.15)	16.62 (−5.81 to 47.85)	0.298
	Travel costs	83	95.07 (45.79)	51	31.11 (11.3)	63.96 (−13.94 to 165.39)	0.128
	Other additional costs	83	766.96 (343.22)	51	346.71 (163.69)	420.26 (−219.52 to 1305.15)	0.27
	Total additional costs	83	884.33 (363.5)	51	389.36 (167.28)	494.96 (−182.1 to 1441.7)	0.192
	3–6 months: total non-NHS and PSS costs	81	905.61 (372.83)	49	399.36 (174.22)	506.25 (−196.78 to 1464.21)	0.204

TABLE 37 Distribution of EQ-5D-5L responses: survivors to hospital discharge

EQ-5D domain	3-month assessment			6-month assessment		
	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]
Mobility, *n* (%)			0.449			0.554
Level 1: no problems	36 (28.1)	31 (34.1)		37 (28.9)	21 (23.1)	
Level 2: slight problems	24 (18.8)	13 (14.3)		11 (8.6)	10 (11)	
Level 3: moderate problems	13 (10.2)	13 (14.3)		11 (8.6)	15 (16.5)	
Level 4: severe problems	7 (5.5)	5 (5.5)		5 (3.9)	1 (1.1)	
Level 5: unable to walk	8 (6.2)	2 (2.2)		10 (7.8)	2 (2.2)	
Missing	40 (31.2)	27 (29.7)		54 (42.2)	42 (46.2)	
Self-care, *n* (%)			0.020			0.420
Level 1: no problems	55 (43)	52 (57.1)		48 (37.5)	36 (39.6)	
Level 2: slight problems	13 (10.2)	2 (2.2)		9 (7)	7 (7.7)	
Level 3: moderate problems	10 (7.8)	5 (5.5)		5 (3.9)	3 (3.3)	
Level 4: severe problems	1 (0.8)	1 (1.1)		2 (1.6)	0 (0)	
Level 5: unable to wash or dress	9 (7)	4 (4.4)		10 (7.8)	3 (3.3)	
Missing	40 (31.2)	27 (29.7)		54 (42.2)	42 (46.2)	
Usual activities, *n* (%)			0.161			0.547
Level 1: no problems	25 (19.5)	26 (28.6)		25 (19.5)	20 (22)	
Level 2: slight problems	25 (19.5)	16 (17.6)		17 (13.3)	11 (12.1)	
Level 3: moderate problems	15 (11.7)	13 (14.3)		16 (12.5)	11 (12.1)	
Level 4: severe problems	6 (4.7)	1 (1.1)		2 (1.6)	2 (2.2)	
Level 5: unable to perform usual activities	17 (13.3)	8 (8.8)		14 (10.9)	5 (5.5)	
Missing	40 (31.2)	27 (29.7)		54 (42.2)	42 (46.2)	
Pain/discomfort, *n* (%)			0.814			0.299
Level 1: no pain or discomfort	37 (28.9)	29 (31.9)		28 (21.9)	24 (26.4)	
Level 2: slight pain or discomfort	25 (19.5)	19 (20.9)		25 (19.5)	13 (14.3)	
Level 3: moderate pain or discomfort	18 (14.1)	8 (8.8)		14 (10.9)	8 (8.8)	
Level 4: severe pain or discomfort	4 (3.1)	5 (5.5)		5 (3.9)	3 (3.3)	
Level 5: extreme pain or discomfort	4 (3.1)	3 (3.3)		2 (1.6)	1 (1.1)	
Missing	40 (31.2)	27 (29.7)		54 (42.2)	42 (46.2)	

continued

TABLE 37 Distribution of EQ-5D-5L responses: survivors to hospital discharge (*continued*)

EQ-5D domain	3-month assessment			6-month assessment		
	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]
Anxiety/depression, *n* (%)			1			0.757
Level 1: not anxious or depressed	40 (31.2)	29 (31.9)		28 (21.9)	21 (23.1)	
Level 2: slightly anxious or depressed	22 (17.2)	17 (18.7)		25 (19.5)	16 (17.6)	
Level 3: moderately anxious or depressed	15 (11.7)	13 (14.3)		12 (9.4)	8 (8.8)	
Level 4: severely anxious or depressed	8 (6.2)	4 (4.4)		4 (3.1)	0 (0)	
Level 5: extremely anxious or depressed	3 (2.3)	1 (1.1)		4 (3.1)	4 (4.4)	
Missing	40 (31.2)	27 (29.7)		55 (43)	42 (46.2)	

a Based on the chi-squared test of differences between proportions.

TABLE 38 Distribution of SF-12 responses: survivors to hospital discharge

SF-12 domain	3-month assessment			6-month assessment		
	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]
General health, *n* (%)			0.590			0.693
Excellent	5 (3.9)	6 (6.6)		4 (3.1)	1 (1.1)	
Very good	10 (7.8)	16 (17.6)		8 (6.2)	13 (14.3)	
Good	32 (25)	24 (26.4)		29 (22.7)	15 (16.5)	
Fair	22 (17.2)	10 (11)		22 (17.2)	12 (13.2)	
Poor	17 (13.3)	7 (7.7)		14 (10.9)	7 (7.7)	
Missing	42 (32.8)	28 (30.8)		51 (39.8)	43 (47.3)	
Moderate activities, *n* (%)			0.321			1
Yes, limited a lot	31 (24.2)	17 (18.7)		21 (16.4)	14 (15.4)	
Yes, limited a little	26 (20.3)	18 (19.8)		25 (19.5)	18 (19.8)	
No, not limited at all	29 (22.7)	28 (30.8)		30 (23.4)	17 (18.7)	
Missing	42 (32.8)	28 (30.8)		52 (40.6)	42 (46.2)	
Climbing stairs, *n* (%)			0.171			0.970
Yes, limited a lot	38 (29.7)	20 (22)		26 (20.3)	16 (17.6)	
Yes, limited a little	19 (14.8)	16 (17.6)		26 (20.3)	19 (20.9)	
No, not limited at all	29 (22.7)	27 (29.7)		23 (18)	14 (15.4)	
Missing	42 (32.8)	28 (30.8)		53 (41.4)	42 (46.2)	

TABLE 38 Distribution of SF-12 responses: survivors to hospital discharge (*continued*)

SF-12 domain	3-month assessment			6-month assessment		
	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]
Accomplished less physically, *n* (%)			0.519			1
All of the time	19 (14.8)	11 (12.1)		17 (13.3)	11 (12.1)	
Most of the time	11 (8.6)	10 (11)		8 (6.2)	6 (6.6)	
Some of the time	18 (14.1)	14 (15.4)		20 (15.6)	16 (17.6)	
A little of the time	16 (12.5)	8 (8.8)		12 (9.4)	5 (5.5)	
None of the time	19 (14.8)	21 (23.1)		19 (14.8)	11 (12.1)	
Missing	45 (35.2)	27 (29.7)		52 (40.6)	42 (46.2)	
Limited physically, *n* (%)			0.193			0.786
All of the time	23 (18)	11 (12.1)		18 (14.1)	14 (15.4)	
Most of the time	9 (7)	7 (7.7)		8 (6.2)	7 (7.7)	
Some of the time	16 (12.5)	17 (18.7)		18 (14.1)	13 (14.3)	
A little of the time	19 (14.8)	8 (8.8)		13 (10.2)	4 (4.4)	
None of the time	16 (12.5)	21 (23.1)		16 (12.5)	11 (12.1)	
Missing	45 (35.2)	27 (29.7)		55 (43)	42 (46.2)	
Did less work,[b] *n* (%)			0.691			1
All of the time	5 (3.9)	6 (6.6)		13 (10.2)	9 (9.9)	
Most of the time	8 (6.2)	3 (3.3)		7 (5.5)	2 (2.2)	
Some of the time	12 (9.4)	12 (13.2)		15 (11.7)	12 (13.2)	
A little of the time	20 (15.6)	9 (9.9)		13 (10.2)	5 (5.5)	
None of the time	33 (25.8)	32 (35.2)		29 (22.7)	21 (23.1)	
Missing	50 (39.1)	29 (31.9)		51 (39.8)	42 (46.2)	
Accomplished less emotionally, *n* (%)			0.495			0.885
All of the time	3 (2.3)	5 (5.5)		14 (10.9)	8 (8.8)	
Most of the time	4 (3.1)	2 (2.2)		7 (5.5)	2 (2.2)	
Some of the time	8 (6.2)	10 (11)		10 (7.8)	10 (11)	
A little of the time	16 (12.5)	7 (7.7)		11 (8.6)	6 (6.6)	
None of the time	46 (35.9)	38 (41.8)		30 (23.4)	22 (24.2)	
Missing	51 (39.8)	29 (31.9)		56 (43.8)	43 (47.3)	
Pain, *n* (%)			0.603			1
Not at all	39 (30.5)	26 (28.6)		32 (25)	21 (23.1)	
A little bit	20 (15.6)	17 (18.7)		17 (13.3)	10 (11)	
Moderately	10 (7.8)	12 (13.2)		8 (6.2)	8 (8.8)	
Quite a bit	8 (6.2)	7 (7.7)		11 (8.6)	7 (7.7)	
Extremely	6 (4.7)	1 (1.1)		9 (7)	3 (3.3)	
Missing	45 (35.2)	28 (30.8)		51 (39.8)	42 (46.2)	

continued

TABLE 38 Distribution of SF-12 responses: survivors to hospital discharge (*continued*)

SF-12 domain	3-month assessment			6-month assessment		
	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]	Adrenaline arm (*N* = 128)	Placebo arm (*N* = 91)	*p*-value[a]
Calm, *n* (%)			0.385			1
All of the time	11 (8.6)	13 (14.3)		9 (7)	5 (5.5)	
Most of the time	40 (31.2)	34 (37.4)		30 (23.4)	20 (22)	
Some of the time	16 (12.5)	11 (12.1)		22 (17.2)	14 (15.4)	
A little of the time	11 (8.6)	3 (3.3)		11 (8.6)	7 (7.7)	
None of the time	2 (1.6)	2 (2.2)		5 (3.9)	3 (3.3)	
Missing	48 (37.5)	28 (30.8)		51 (39.8)	42 (46.2)	
Energy, *n* (%)			0.178			0.886
All of the time	5 (3.9)	9 (9.9)		3 (2.3)	3 (3.3)	
Most of the time	20 (15.6)	20 (22)		19 (14.8)	13 (14.3)	
Some of the time	21 (16.4)	18 (19.8)		19 (14.8)	17 (18.7)	
A little of the time	20 (15.6)	5 (5.5)		19 (14.8)	6 (6.6)	
None of the time	15 (11.7)	11 (12.1)		17 (13.3)	10 (11)	
Missing	47 (36.7)	28 (30.8)		51 (39.8)	42 (46.2)	
Feeling downhearted, *n* (%)			1			0.859
All of the time	5 (3.9)	3 (3.3)		5 (3.9)	2 (2.2)	
Most of the time	6 (4.7)	3 (3.3)		12 (9.4)	8 (8.8)	
Some of the time	24 (18.8)	17 (18.7)		19 (14.8)	12 (13.2)	
A little of the time	22 (17.2)	19 (20.9)		24 (18.8)	11 (12.1)	
None of the time	24 (18.8)	21 (23.1)		17 (13.3)	16 (17.6)	
Missing	47 (36.7)	28 (30.8)		51 (39.8)	42 (46.2)	
Social activities, *n* (%)			1			0.953
All of the time	10 (7.8)	8 (8.8)		11 (8.6)	6 (6.6)	
Most of the time	10 (7.8)	4 (4.4)		6 (4.7)	6 (6.6)	
Some of the time	19 (14.8)	13 (14.3)		18 (14.1)	10 (11)	
A little of the time	7 (5.5)	10 (11)		9 (7)	7 (7.7)	
None of the time	35 (27.3)	28 (30.8)		33 (25.8)	20 (22)	
Missing	47 (36.7)	28 (30.8)		51 (39.8)	42 (46.2)	

a Based on the chi-squared test of differences between proportions.
b Carried out work or other activities less carefully than usual because of emotional problems.

TABLE 39 Cost-effectiveness results: sensitivity analyses (2017 prices)

	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness		
Analysis model	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (95% CI)	Probability of being cost-effective at £30,000/QALY
Unadjusted multiple imputation	4566 (166)	0.0076 (0.0008)	3229 (166)	0.0067 (0.0008)	1337 (877 to 1797)	0.001 (−0.0012 to 0.0031)	1,401,872	−1308 (−1748 to −868)	0
Adjusted complete case	3082 (369)	−0.0007 (0.002)	2067 (371)	−0.0014 (0.002)	1015 (725 to 1306)	0.0007 (−0.0008 to 0.0023)	1,377,745	−993 (−1270 to −716)	0
Unadjusted complete case	3943 (106)	0.0064 (0.0006)	2905 (106)	0.0057 (0.0006)	1038 (745 to 1332)	0.0007 (−0.0009 to 0.0022)	1,521,586	−1018 (−1297 to −739)	0
Parameter estimates via linear regression implemented within a bootstrap	3592 (522)	0.0024 (0.0025)	2292 (527)	0.0017 (0.0025)	1300 (846 to 1755)	0.0007 (−0.0014 to 0.0029)	1,784,993	−1279 (−1737 to −820)	0
QALYs based on mRS data 6 months	3591 (541)	0.0031 (0.0026)	2285 (545)	0.0018 (0.0026)	1306 (836 to 1776)	0.0012 (−0.001 to 0.0035)	1,069,119	−1269 (−1719 to −819)	0
QALYs derived assuming baseline utility of −0.042 (unconscious state)	3592 (530)	0.0018 (0.0024)	2292 (535)	0.0015 (0.0024)	1300 (839 to 1761)	0.0003 (−0.0018 to 0.0024)	4,218,224	−1291 (−1738 to −844)	0
Societal costs, 6 months	3638 (541)	0.0025 (0.0025)	2228 (545)	0.0017 (0.0026)	1410 (940 to 1880)	0.0008 (−0.0014 to 0.003)	1,828,271	−1387 (−1837 to −937)	
QALYs based on EQ-5D/mRS, 12 months NHS/PSS costs	3741 (536)	0.006 (0.0049)	2330 (541)	0.0038 (0.005)	1411 (946 to 1876)	0.0022 (−0.0021 to 0.0065)	644,308	−1346 (−1784 to −907)	

continued

TABLE 39 Cost-effectiveness results: sensitivity analyses (2017 prices) (*continued*)

	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness		
Analysis model	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (95% CI)	Probability of being cost-effective at £30,000/QALY
QALYs based on mRS data, 12-month NHS/PSS costs	3742 (538)	0.0068 (0.005)	2327 (542)	0.0041 (0.0051)	1415 (948 to 1881)	0.0027 (−0.0017 to 0.007)	528,477	−1334 (−1771 to −898)	0
QALYs based on EQ-5D/mRS data, 12-month societal costs	3768 (571)	0.0059 (0.005)	2259 (576)	0.0037 (0.005)	1509 (1014 to 2004)	0.0022 (−0.0021 to 0.0066)	679,317	−1442 (−1908 to −977)	0
Excluded stand-down and restock time in emergency response cost calculations	2989 (526)	0.002 (0.0025)	1684 (530)	0.0012 (0.0025)	1305 (844 to 1766)	0.0007 (−0.0015 to 0.0029)	1,835,618	−1284 (−1727 to −841)	0
Excluded estimated cost of transporting deceased patients to nearest hospital mortuary if patient died at scene of cardiac arrest and in a public place	3445 (525)	0.0019 (0.0025)	2146 (529)	0.0012 (0.0025)	1299 (838 to 1760)	0.0007 (−0.0014 to 0.0029)	1,794,795	−1277 (−1720 to −835)	0
Excluded stand-down/restock time and cost of transporting patients to nearest mortuary in emergency response cost calculations	2989 (526)	0.002 (0.0025)	1684 (530)	0.0012 (0.0025)	1305 (844 to 1766)	0.0007 (−0.0015 to 0.0029)	1,835,618	−1284 (−1727 to −841)	0

TABLE 40 Sensitivity analyses exploring the impact of missing-not-at-random assumption on the within-trial base-case cost-effectiveness results (imputed utility values were systematically increased/decreased from 0% to 100% of imputed value within the imputation model)

	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness	
Missing-not-at-random assumption	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (95% CI) (£)
Increased imputed utility by								
100%	3601 (529)	0.0022 (0.0036)	2320 (534)	0.0009 (0.0036)	1281 (821 to 1741)	0.0013 (−0.0018 to 0.0043)	1,021,684	−1243 (−1681 to −805)
75%	3594 (534)	0.0021 (0.0033)	2307 (538)	0.0009 (0.0034)	1287 (823 to 1750)	0.0012 (−0.0017 to 0.0041)	1,072,646	−1251 (−1693 to −808)
50%	3606 (530)	0.0022 (0.0031)	2322 (534)	0.001 (0.0031)	1284 (823 to 1744)	0.0011 (−0.0015 to 0.0038)	1,120,679	−1249 (−1689 to −810)
25%	3595 (540)	0.0024 (0.0029)	2302 (545)	0.0012 (0.0029)	1294 (824 to 1763)	0.0011 (−0.0014 to 0.0036)	1,158,930	−1260 (−1709 to −811)
0.0%	3582 (532)	0.0024 (0.0025)	2292 (537)	0.0016 (0.0025)	1291 (828 to 1754)	0.0008 (−0.0014 to 0.003)	1,670,014	−1268 (−1712 to −823)
Decreased imputed utility by								
25%	3594 (522)	0.0027 (0.0023)	2298 (527)	0.002 (0.0023)	1296 (842 to 1750)	0.0006 (−0.0013 to 0.0026)	2,036,654	−1277 (−1717 to −837)
50%	3580 (538)	0.0026 (0.0023)	2262 (543)	0.002 (0.0023)	1318 (850 to 1786)	0.0006 (−0.0014 to 0.0026)	2,114,049	−1299 (−1753 to −845)
75%	3574 (539)	0.0027 (0.0023)	2269 (543)	0.002 (0.0023)	1305 (837 to 1773)	0.0006 (−0.0014 to 0.0026)	2,067,739	−1286 (−1740 to −832)
100%	3574 (539)	0.0027 (0.0023)	2269 (543)	0.002 (0.0023)	1305 (837 to 1773)	0.0006 (−0.0014 to 0.0026)	2,067,739	−1286 (−1740 to −832)

TABLE 41 Sensitivity analyses exploring the impact of missing-not-at-random assumption on the within-trial base-case cost-effectiveness results (imputed costs were systematically increased/decreased from 0% to 100% of imputed value within the imputation model)

	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness	
Missing-not-at-random assumption	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (£)
Increased imputed costs by								
100%	3175 (874)	0.0024 (0.0028)	2285 (881)	0.0017 (0.0028)	890 (131 to 1650)	0.0008 (–0.0017 to 0.0032)	1,186,037	0.008
75%	3196 (802)	0.0024 (0.0027)	2238 (808)	0.0017 (0.0027)	958 (261 to 1655)	0.0007 (–0.0016 to 0.0031)	1,301,145	0.003
50%	3300 (703)	0.0025 (0.0026)	2331 (709)	0.0017 (0.0026)	969 (358 to 1580)	0.0008 (–0.0015 to 0.0031)	1,246,202	0
25%	3384 (621)	0.0024 (0.0026)	2335 (626)	0.0017 (0.0026)	1049 (509 to 1589)	0.0008 (–0.0015 to 0.003)	1,363,580	0
0.0%	3582 (532)	0.0024 (0.0025)	2292 (537)	0.0016 (0.0025)	1291 (828 to 1754)	0.0008 (–0.0014 to 0.003)	1,670,014	0
Decreased imputed costs by								
25%	3634 (516)	0.0024 (0.0025)	2299 (520)	0.0017 (0.0025)	1335 (887 to 1783)	0.0008 (–0.0014 to 0.0029)	1,746,277	0
50%	3650 (507)	0.0024 (0.0025)	2334 (512)	0.0017 (0.0025)	1315 (874 to 1756)	0.0008 (–0.0014 to 0.0029)	1,687,983	0
75%	3663 (511)	0.0024 (0.0025)	2359 (515)	0.0016 (0.0025)	1304 (860 to 1747)	0.0008 (–0.0014 to 0.0029)	1,688,008	0
100%	3663 (511)	0.0024 (0.0025)	2359 (515)	0.0016 (0.0025)	1304 (860 to 1747)	0.0008 (–0.0014 to 0.0029)	1,688,008	0

TABLE 42 Cost-effectiveness results: subgroup analyses (2017 prices)

Subgroup	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness		
	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (95% CI) (£)	Probability of being cost-effective at £30,000/QALY
Cause of cardiac arrest									
Non-medical	3491 (660)	0.0014 (0.0031)	2403 (702)	0.0029 (0.0033)	1088 (−563 to 2740)	−0.0015 (−0.0092 to 0.0062)	Dominated	−1134 (−2722 to 455)	0.079
Medical	3763 (383)	0.005 (0.0018)	2438 (702)	0.004 (0.0033)	1325 (−1062 to 3713)	0.001 (−0.0102 to 0.0122)	1,356,042	−1296 (−3702 to 1110)	0.147
Age (years)									
≤ 60	5550 (552)	0.0087 (0.0026)	3234 (561)	0.0059 (0.0026)	2316 (1614 to 3018)	0.0028 (−0.0005 to 0.0061)	823,606	−2232 (−2906 to −1557)	0
> 60	2729 (570)	0.0001 (0.0027)	2272 (561)	0.0011 (0.0026)	457 (−722 to 1636)	−0.001 (−0.0065 to 0.0046)	Dominated	−486 (−1660 to 688)	0.195
Sex									
Female	3434 (563)	0.0022 (0.0026)	2432 (565)	0.002 (0.0026)	1002 (213 to 1790)	0.0002 (−0.0034 to 0.0039)	4,145,700	−995 (−1753 to −236)	0.004
Male	3690 (521)	0.0035 (0.0024)	2220 (565)	0.0024 (0.0026)	1470 (213 to 2728)	0.0011 (−0.0048 to 0.0069)	1,389,015	−1439 (−2696 to −182)	0.016
EMS time from arrival at scene to administration of first dose (minutes)									
≤ 10	3399 (600)	0.0031 (0.0028)	2478 (605)	0.001 (0.0028)	922 (−72 to 1916)	0.0021 (−0.0026 to 0.0067)	439,679	−859 (−1815 to 97)	0.04
> 10	3220 (531)	−0.0037 (0.0025)	1795 (605)	−0.0041 (0.0028)	1425 (−86 to 2937)	0.0004 (−0.0067 to 0.0074)	3,989,128	−1415 (−2931 to 102)	0.027

continued

TABLE 42 Cost-effectiveness results: subgroup analyses (2017 prices) (*continued*)

	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness		
Subgroup	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (95% CI) (£)	Probability of being cost-effective at £30,000/QALY
Time from 999 call received to EMS arrival at scene (minutes)									
≤ 10	3676 (544)	0.0024 (0.0025)	2203 (548)	0.0018 (0.0026)	1473 (925 to 2021)	0.0006 (−0.002 to 0.0032)	2,427,288	−1455 (−1982 to −927)	0
> 10	2188 (599)	−0.001 (0.0028)	1335 (548)	−0.0022 (0.0026)	853 (−336 to 2042)	0.0012 (−0.0043 to 0.0068)	701,635	−817 (−1985 to 352)	0.086
Shockable rhythm									
No	3435 (548)	0.0025 (0.0026)	2425 (552)	0.0017 (0.0026)	1010 (483 to 1536)	0.0008 (−0.0016 to 0.0033)	1,201,680	−984 (−1491 to −478)	0
Yes	9166 (684)	0.0306 (0.0032)	6620 (552)	0.0302 (0.0026)	2546 (1236 to 3857)	0.0005 (−0.0057 to 0.0066)	5,282,677	−2532 (−3813 to −1251)	0.001
Number of syringes given (out of two)									
≤ 2	9767 (751)	0.0238 (0.0035)	7641 (827)	0.0319 (0.0039)	2127 (690 to 3564)	−0.008 (−0.0148 to -0.0013)	Dominated	−2367 (−3758 to −977)	0.001
> 2	2031 (637)	−0.0029 (0.003)	1347 (827)	−0.0032 (0.0039)	685 (−1432 to 2801)	0.0002 (−0.0097 to 0.0102)	2,995,310	−678 (−2809 to 1453)	0.269
Number of syringes given (out of four)									
≤ 4	5315 (556)	0.0081 (0.0026)	3036 (572)	0.0068 (0.0027)	2279 (1582 to 2976)	0.0013 (−0.002 to 0.0046)	1,782,438	−2241 (−2912 to −1569)	0
> 4	936 (573)	−0.0068 (0.0027)	686 (572)	−0.0061 (0.0027)	251 (−920 to 1422)	−0.0007 (−0.0062 to 0.0048)	Dominated	−272 (−1439 to 896)	0.319

Subgroup	Adrenaline arm		Placebo arm		Mean difference (95% CI)		Cost-effectiveness		
	Mean costs (SE) (£)	Mean QALYs (SE)	Mean costs (SE) (£)	Mean QALYs (SE)	Costs (£)	QALYs	ICER (£/QALY)	INMB at £30,000/QALY (95% CI) (£)	Probability of being cost-effective at £30,000/QALY
Witnessed by									
Not witnessed	3470 (560)	0.002 (0.0026)	2409 (568)	0.0022 (0.0027)	1061 (299 to 1823)	−0.0002 (−0.0038 to 0.0034)	Dominated	−1067 (−1800 to −334)	0.002
EMS	4738 (787)	0.0117 (0.0037)	3804 (568)	0.0125 (0.0027)	934 (−829 to 2696)	−0.0009 (−0.0091 to 0.0074)	Dominated	−959 (−2687 to 768)	0.153
Bystander	4762 (572)	0.0068 (0.0027)	3189 (568)	0.0049 (0.0027)	1573 (308 to 2837)	0.0019 (−0.0041 to 0.0078)	843,463	−1517 (−2777 to −256)	0.007
Bystander CPR									
No	3325 (582)	0.0032 (0.0027)	2411 (545)	0.0029 (0.0026)	915 (−219 to 2048)	0.0003 (−0.005 to 0.0056)	2,859,086	−905 (−2026 to 216)	0.048
Yes	4022 (538)	0.0033 (0.0025)	2456 (545)	0.0022 (0.0026)	1566 (964 to 2169)	0.0011 (−0.0018 to 0.0039)	1,475,919	−1535 (−2114 to −955)	0

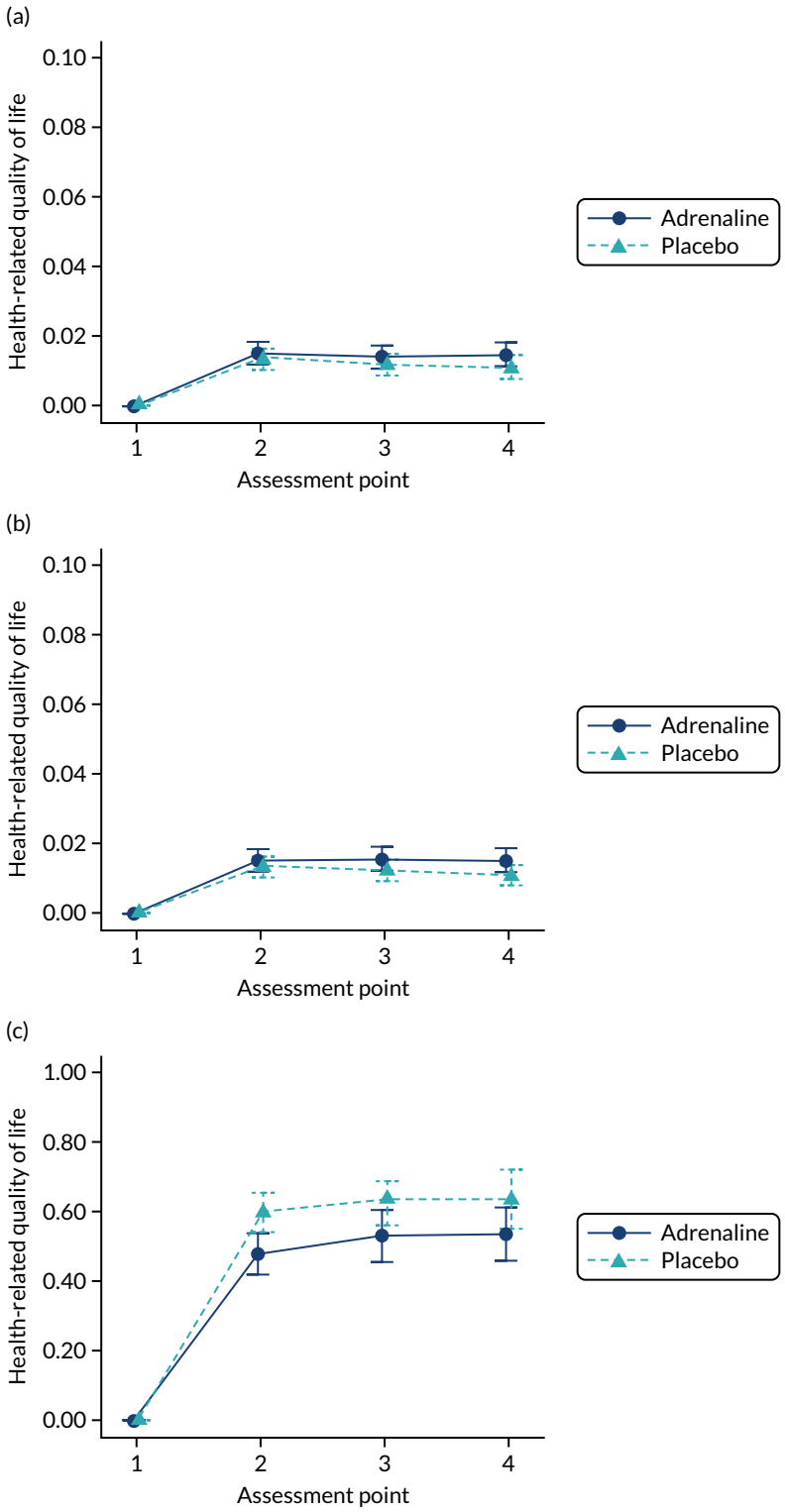

FIGURE 25 Health-related quality of life at baseline, at hospital discharge and at 3 and 6 months after randomisation. (a) EQ-5D/mRS (whole trial); (b) mRS (whole trial); (c) EQ-5D/mRS (survivors); and (d) mRS (survivors). (*continued*)

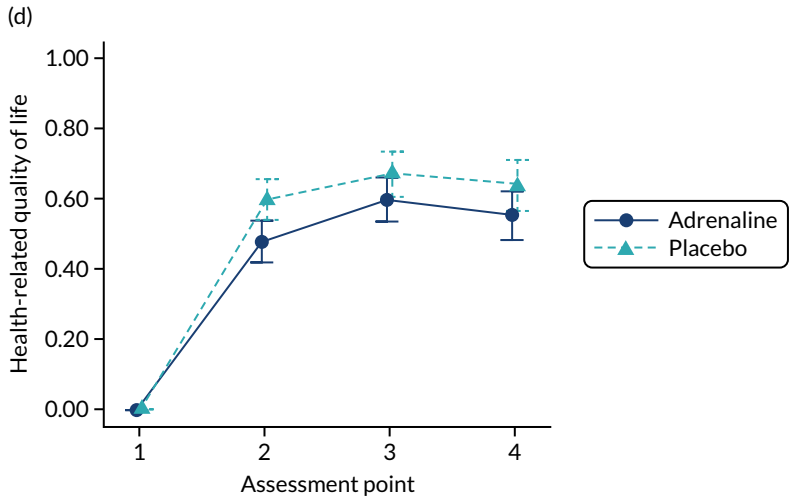

FIGURE 25 Health-related quality of life at baseline, at hospital discharge and at 3 and 6 months after randomisation. (a) EQ-5D/mRS (whole trial); (b) mRS (whole trial); (c) EQ-5D/mRS (survivors); and (d) mRS (survivors).

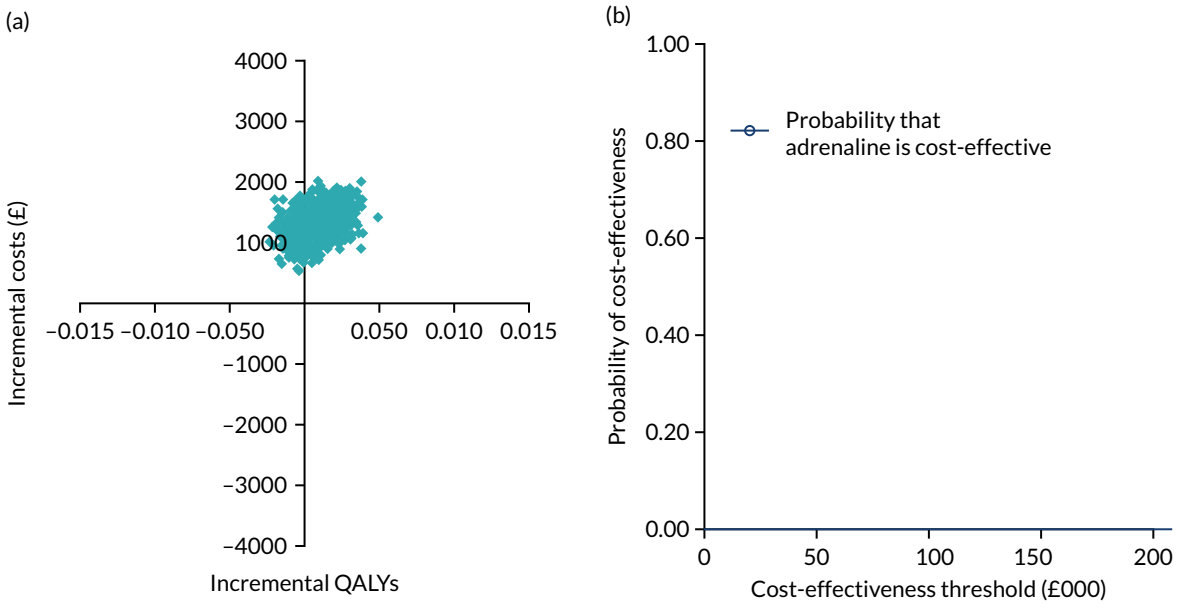

FIGURE 26 Adjusted multiple imputation (base case). (a) Cost-effectiveness plane; and (b) CEAC.

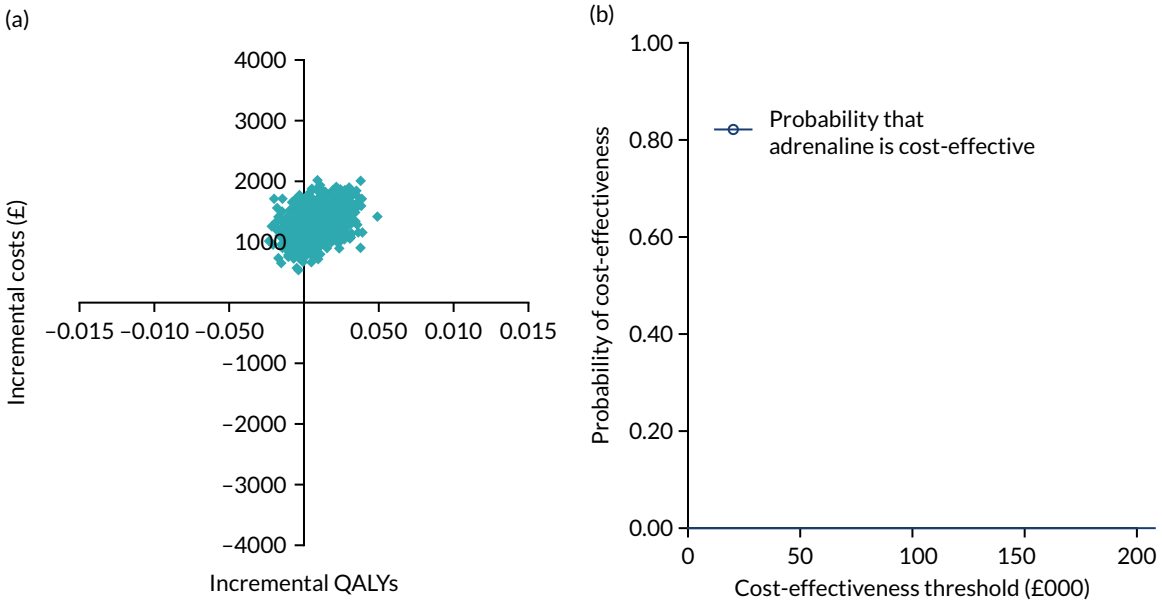

FIGURE 27 The 12-month time horizon (QALYs based on EQ-5D-5L and mRS data, NHS/PSS costs). (a) Cost-effectiveness plane; and (b) CEAC.

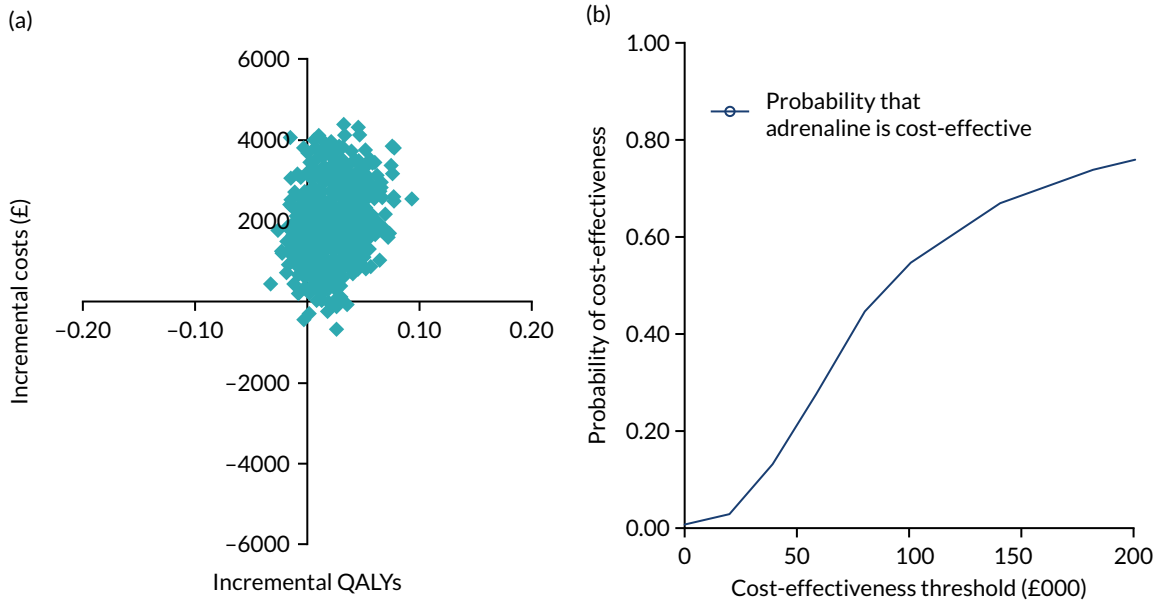

FIGURE 28 The lifetime time horizon (QALYs based on mRS data, NHS/PSS costs). (a) Cost-effectiveness plane; and (b) CEAC.

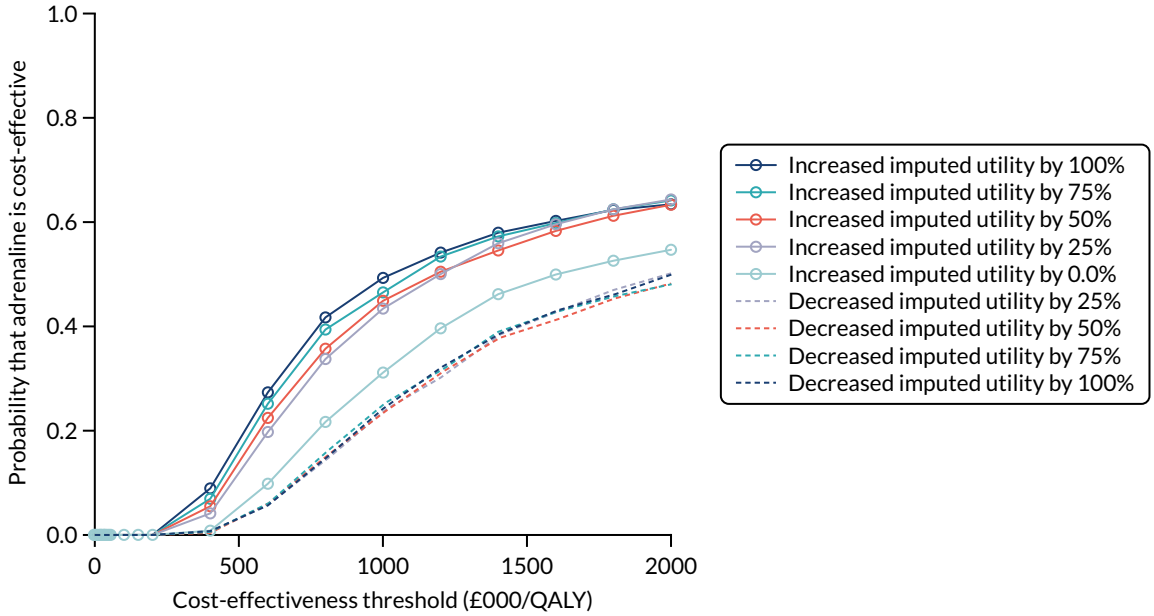

FIGURE 29 The CEAC from sensitivity analyses assessing the impact of missing-not-at-random assumptions on imputed utilities (QALYs based on mRS data, NHS/PSS costs over 6 months).

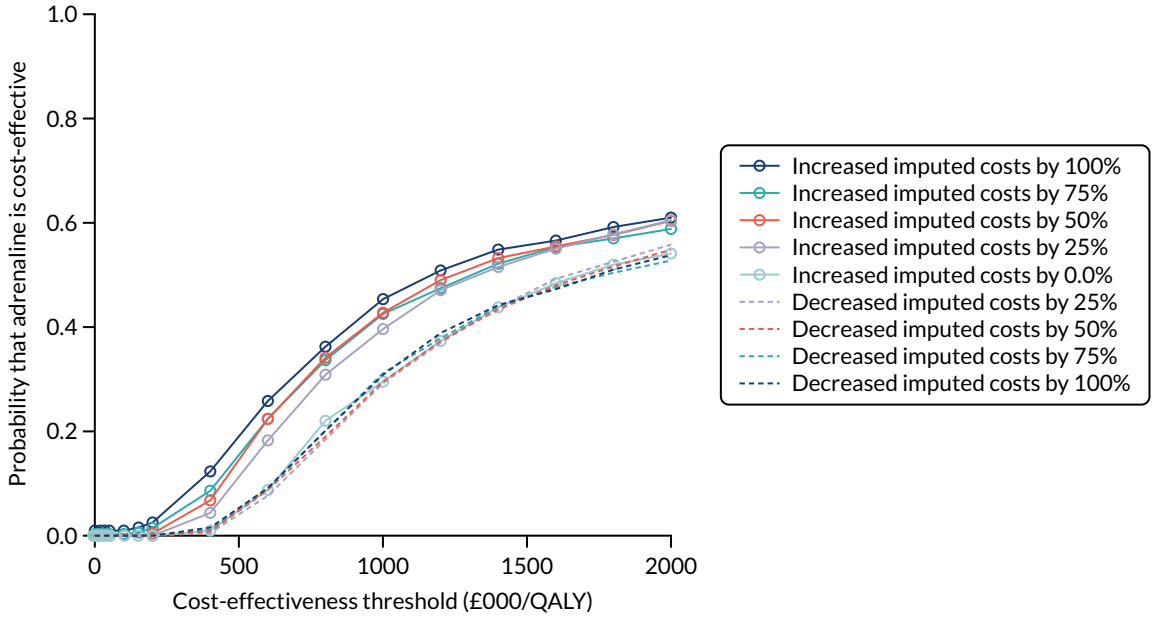

FIGURE 30 The CEAC from sensitivity analyses assessing the impact of missing-not-at-random assumptions on imputed costs (QALYs based on mRS data, NHS/PSS costs over 6 months).

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