**Title:**

Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients
aged 65 years or over with vasodilatory hypotension: Statistical and Health Economic Analysis Plan for the 65 trial

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# Abstract

The 65 trial is a pragmatic, multicentre, parallel-group, open-label, randomised clinical trial of permissive hypotension (targeting a mean arterial pressure target of 60 – 65 mmHg during vasopressor therapy) versus usual care in critically ill patients aged 65 years or over with vasodilatory hypotension. The trial will recruit 2,600 patients from 65 United Kingdom adult, general critical care units. The primary outcome is all-cause mortality at 90 days. An economic evaluation is embedded. This paper describes the proposed statistical and health economic analysis for the 65 trial.

## Trial registration

ISRCTN10580502

## Key words:

Vasopressors, mean arterial pressure, critical care, intensive care, health economics, clinical trial, statistical analysis plan

# Introduction

## Background and rationale

In critically ill patients, hypotension (low blood pressure) is common, especially in patients with severe infections. Increasing blood pressure is a complex process involving multiple interventions including vasopressors (intravenous drugs), fluids and catheters. Vasopressors, which cause vasoconstriction and may increase cardiac workload, are a mainstay of treatment.

The 65 trial is a randomised controlled trial to evaluate the clinical and cost-effectiveness of targeting an increase in blood pressure to targets slightly below conventional levels (permissive hypotension), in comparison with usual care. For more details on the background and rationale of the proposed intervention and, for a full explanation of the trial design, please see the protocol, which has been submitted for publication in parallel with this paper. A brief outline is presented below.

This paper describes the proposed statistical analyses for the 65 trial, and has been prepared in accordance with recent published guidelines[[1]](#endnote-1) and includes a fully integrated economic evaluation.

## Objectives

To estimate the clinical and cost-effectiveness of permissive hypotension (targeting a mean arterial pressure [MAP] range 60-65 mmHg while receiving vasopressors) in critically ill patients aged 65 years or over with vasodilatory hypotension compared with usual care.

# Study Methods

## Trial design

The 65 trial is a pragmatic, multi-centre, parallel group randomised clinical trial (RCT). Treatment allocation is a 1:1 ratio. Patients are randomised to either permissive hypotension (targeting a MAP range 60-65 mmHg while receiving vasopressors) or usual care, with randomisation by permuted blocks (with variable block length) stratified by site.

## Sample size

In the original protocol, the sample size was calculated as follows: assuming 90-day mortality of 35% within usual clinical care (based on data from the Case Mix Programme [CMP] – the national clinical audit of adult critical care in England, Wales and Northern Ireland – for patients aged 65 years or older admitted to critical care and receiving advanced cardiovascular support as defined according to the UK Department of Health Critical Care Minimum Dataset (CCMDS)), a sample size of 1402 patients provided 90% power to detect as statistically significant (P<0.05) an 8% absolute risk reduction to 27%. Allowing for 2.5% withdrawal/loss to follow up, we aimed to recruit a total of 1440 patients. In a substantial amendment to the protocol, the detectable absolute risk reduction was changed from 8% to 6% (corresponding to 90-day mortality of 29% in the intervention group, with all other parameters remaining unchanged) leading to a revised sample size of 2,600 (1,300 per group). This change was recommended by the Trial Steering Committee after the internal pilot stage feasibility assessment when the duration of vasopressors in the control group was recorded as lower than expected, suggesting that the difference in treatment (and hence outcome) between groups may be smaller than initially anticipated.

## Statistical interim analyses and stopping guidance

A feasibility assessment was conducted after the end of the internal pilot stage (first six months of the trial recruitment period) against the following progression criteria:

* separation between groups of 10mg (norepinephrine equivalent) in mean total vasopressor dose and/or a separation of 5mmHg in peak MAP whilst receiving vasopressors;
* a minimum of 50 sites open to recruitment; and
* recruitment rate in open sites at least 80% of anticipated.

The feasibility assessment recommended continuation, with modified inclusion criteria and increased sample size.

A single interim analysis of 90-day mortality was performed following the recruitment, and follow-up to 90 days, of 500 patients, and reviewed by the Data Monitoring and Ethics Committee (DMEC). The interim analysis was conducted using a Peto-Haybittle stopping rule (P<0.001) to guide recommendations for early termination due to either effectiveness or harm. The Trial Statistician, Senior Statistician and DMEC were not blinded to treatment allocation. All other investigators remain unaware of the results of the interim analysis, other than the recommendation from the DMEC to continue recruitment.

## Timing of final analysis

The end of the trial will be when all patients recruited in the first fourteen months of the recruitment period have completed one-year follow-up and the final patient recruited has completed 90-day follow-up. Following the end of the trial, any patients remaining in long-term follow-up will be censored, the trial database will be locked and the final analyses conducted.

## Timing of outcome assessments

The timing for all outcome assessments are taken relative to the date of randomisation. Patients surviving to 90 days and one year will be followed up with a questionnaire, providing their one-year follow-up time is reached prior to the end of the trial (as defined above).

# Statistical Principles

## Confidence intervals and P values

All statistical tests will be for superiority and will be two-sided with significance set at P<0.05. Effect estimates will be reported with 95% confidence intervals. There will be no adjustment for multiple testing. The results of any subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects[[2]](#endnote-2),[[3]](#endnote-3).

## Adherence and protocol deviations

### Exposure

Exposure to the intervention will be assessed by the following parameters, which will be summarised by treatment group using descriptive statistics (mean, standard deviation, median and interquartile range (IQR), or counts and percentages for binary variables) and as a difference in means between treatment groups with 95% confidence interval:

* MAP –the highest and mean MAP over time for each patient while receiving vasopressors;
* receipt of vasopressors – the number and percentage of patients receiving each vasopressor - either as a continuous infusion or bolus (norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin, metaraminol, terlipressin);
* duration of vasopressors, in hours, from the later of either time of randomisation or time of initiation of vasopressors to the end of the first episode of vasopressors (defined as the start of a 24-hour period during which the patient received no vasopressors), critical care discharge or death (whichever of the latter is first);
* dose-rate of vasopressors when given as a continuous infusion –the highest and mean rate of norepinephrine equivalents (μg kg−1 min−1) and metaraminol (mg h−1); and
* total dose of vasopressors (from either infusion or bolus) – reported as the median dose among patients receiving the relevant vasopressors and mean (with a value of 0 for patients not receiving the vasopressor) among all patients, separately for norepinephrine equivalent, metaraminol, and terlipressin.

Norepinephrine equivalents will be calculated using two alternate conversion methods, as summarised in Table 14,5.

**Table 1. Alternate conversion methods for calculating norepinephrine equivalents**

|  |  |  |
| --- | --- | --- |
| **Vasopressor** | **Unit** | **Conversion factor for norepinephrine equivalent** |
| ***Method 1[[4]](#endnote-4)*** |  |  |
| Epinephrine | μg kg−1 min−1 | ×1 |
| Dopamine | μg kg−1 min−1 | x1/150 |
| Phenylephrine | μg kg−1 min−1 | ×0.1 |
| Vasopressin | U min−1 | ×2.5 |
| ***Method 2***[[5]](#endnote-5) |  |  |
| Epinephrine | μg kg−1 min−1 | ×1 |
| Dopamine | μg kg−1 min−1 | ×0.01 |
| Phenylephrine | μg kg−1 min−1 | ×0.45 |
| Vasopressin | U min−1 | ×5×100/weight (kg) |

Data on vasopressor infusions are collected hourly. Accordingly, to calculate total dose, each recorded infusion episode is assumed to last for exactly one hour. Analysis using the calculations from Method 1 of Table 1 will be used for the main results paper for this trial and the corresponding analysis using calculations from Method 2 will be available in a supplementary appendix.

A number of different graphical approaches will be used to visually summarise treatment pathways by group. These will not incorporate any formal statistical comparisons beyond those specified in this SAP.

### Protocol deviations

The number and percentage of patients found to have been ineligible following randomisation will be reported in each treatment group, together with the reasons for ineligibility (inclusion criteria not met or exclusion criteria met).

Failure to discontinue vasopressors or reduce the dose-rate once MAP is above the upper limit of the MAP target range (65mmHg) for at least three hours in the permissive hypotension group defines a potential protocol deviation (i.e. there can be no treatment protocol deviation in the usual care group). Potential protocol deviations, identified from trial data, trigger a query to the participating site who have the opportunity to provide a justification. In some cases (for example, MAP values may have been above range only transiently on the hour but within range between the hourly recordings in the trial data), the Trial Management Group will determine whether, or not, that the event did constitute a protocol deviation. The total number of such events which were decided not to constitute a deviation will be reported.

The number and percentage of patients with at least one protocol deviation in the permissive hypotension group will be reported. Adherence will be defined at the patient level as having or not having experienced a protocol deviation.

For each patient in the permissive hypotension group, the following measures of protocol adherence will also be calculated: total time on vasopressors with recorded MAP within target range; total time on vasopressors with recorded MAP above target range; total time on vasopressors with recorded MAP more than 5 mmHg above upper limit of target; and total time on vasopressors with recorded MAP below target range. These measures will be summarised as mean, standard deviation, median and IQR.

## Analysis populations

All analyses will adhere to the intention-to-treat principle. The patients will be analysed according to the initial treatment group assignment, irrespective of whether the allocated treatment was received. All patients for whom the primary outcome is known will be included in the analyses, regardless of protocol adherence.

# Trial Population

## Screening data

The following summaries of screening data will be presented:

* total number of days screening;
* number of screened patients;
* number of eligible patients (% of screened patients);
* number of recruited patients (% of eligible patients) and reasons for non-recruitment; and, where known,
* mean overall recruitment rate per month (defined as number of recruited patients/(total number of days screening×12/365) and median of the monthly recruitment rate calculated by site.

## Eligibility

Full details of the eligibility criteria can be found in the 65 trial protocol.

Among those screened, the number and percentage of patients ineligible due to: (1) receiving noradrenaline at <0.1 μg kg−1 min−1; (2) vasopressors not expected to continue for six hours or more; and (3) meeting each of the exclusion criteria will be reported.

## Recruitment

A CONSORT flow diagram[[6]](#endnote-6) will be used to summarise the number of patients who were:

* assessed for eligibility at screening;
* eligible at screening;
* ineligible at screening (with reasons);
* eligible and randomised;
* eligible but not randomised (with reasons);
* lost to follow-up (with reasons);
* included in the primary analysis; and
* excluded from the primary analysis (with reasons).

The 65 trial has been granted an emergency waiver of consent by the research ethics committee and patients, or their Consultees, are approached for consent/opinion following randomisation and once the patients’ medical situation is deemed to be no longer an emergency. Patients, or their Consultees, are asked to consent separately to each of the following components of the trial: continued trial participation (e.g. trial treatment); access to medical notes; follow-up questionnaires; their GP being informed; and use of their information to support future research.

The number and percentage of patients that had capacity at randomisation and gave consent will be reported for each treatment group. Subsequent consent procedures will be summarised in a flow diagram including the following information for each treatment group.

* For all patients:
	+ whether a Consultee (personal or nominated) was approached; or
	+ whether the patient regained capacity prior to a Consultee being approached.
* For those where a Consultee was approached:
	+ whether the Consultee gave agreement to continue trial participation, access to medical records and for the patient to receive follow-up questionnaires or any other outcome of the approach; and
	+ whether the patient regained capacity before hospital discharge.
* For those that regained capacity:
	+ whether the patient gave consent to continue trial participation, access to medical records and to receive follow-up questionnaires or any other outcome of the approach.
* For those that were discharged prior to consent/opinion being confirmed in hospital, the telephone/postal approach for consent/opinion will be summarised

## Withdrawal/Follow-up

Patients (or their Consultees) may withdraw consent from all components, including trial participation, or they may withdraw from questionnaire follow-up alone.

The number and percentage of patients withdrawing consent (or Consultees withdrawing agreement) to trial participation will be reported in each group, with reasons where provided. Data collected up until the point of withdrawal will be included in the analyses, but no further data will be collected for that patient.

The number and percentage of patients lost to follow-up for mortality (as a percentage of all randomised patients) and for questionnaire response (as a percentage of survivors) at 90 days and at one year will be reported in each group.

The total lost to follow-up for mortality will include both consented patients for whom data are unavailable (true loss to follow-up), and those who withdrew and those for whom consent to access medical notes was never given.

The total loss to follow-up for 90-day questionnaires will include both consented patients for whom data are unavailable (true loss to follow-up), and for those who withdrew from trial participation or follow-up, and for those for whom consent to receive questionnaires was never provided.

## Baseline patient characteristics

The following baseline demographic and clinical data will be summarised for each treatment group but not subjected to statistical testing. Categorical variables will be summarised as counts and percentages, continuous variables will be summarised as mean (standard deviation) or median (IQR):

* Demographics -
	+ age
	+ sex (male, female);
* Comorbidities -
	+ chronic hypertension (yes, no)
	+ chronic heart failure (yes, no)
	+ atherosclerotic disease (yes, no);
* Dependency prior to admission to acute hospital (able to live without assistance in daily activities, minor/major assistance with daily activities, total assistance with all daily activities);
* Location prior to admission to critical care and urgency of surgery (ED/not in hospital, theatre-elective/scheduled surgery, theatre-emergency/urgent surgery, other critical care unit, ward or intermediate care area);
* Acute severity of illness from first 24 hours following admission to the unit -
	+ APACHE II Score[[7]](#endnote-7)
	+ ICNARC Physiology Score[[8]](#endnote-8)
	+ ICNARC*H*-2015 model predicted risk of death[[9]](#endnote-9);
* Sepsis-3[[10]](#endnote-10) , [[11]](#endnote-11)(no sepsis, sepsis, septic shock);
* MAP (mmHg) at randomisation;
* Vasopressors received as a continuous infusion at randomisation -
	+ none\*
	+ Norepinephrine equivalent < 0.1 μg kg−1 min−1†
	+ Norepinephrine equivalent ≥ 0.1 μg kg−1 min−1
	+ Metaraminol
	+ other/combination;
* Duration of vasopressors prior to randomisation (minutes).

\*Patients in this category were eligible for recruitment, prior to Version 2.0 of the protocol if a decision had been taken to start vasopressors or if they had received vasopressors in the form of metaraminol or terlipressin boluses.

†Patients in this category were eligible for recruitment prior to Version 2.0 of the protocol

The baseline characteristics of patients completing a follow-up questionnaire at 90 days will be compared with those for patients known to be alive at 90 days who did not complete a follow-up questionnaire. The same approach will be taken for one-year questionnaires (noting that one-year follow-up is truncated).

# Clinical Effectiveness Analysis

## Primary clinical outcome

The primary clinical outcome is 90-day mortality, defined as death due to any cause by 90 days following randomisation.

## Secondary clinical outcomes

### Mortality at discharge from the critical care unit and acute hospital

Mortality at discharge from the critical care unit is defined as death due to any cause before discharge to any location providing a level of care less than Level 2 (high dependency care). Mortality at discharge from acute hospital will be defined as death due to any cause before discharge from acute hospital. Patients transferred from the original acute hospital to another acute hospital will be followed up until they are discharged from acute hospital.

### Duration of survival to longest available follow-up

Duration of survival will be calculated as the duration, in days, from the date of randomisation to the date of death. Patients will be censored at the last date on which they were known to be alive.

### Duration of advanced respiratory and renal support during the critical care unit stay

Advanced respiratory support will be defined according to the CCMDS. The duration of organ support will be defined as the number of calendar days (00:00 to 23:59) on which the organ support was received at any time during that day. Any days after discharge from critical care will be assumed to be free of organ support. Duration of renal support will be defined in the same way. Patients who are transferred directly from the original critical care unit to another critical care unit also participating in the CMP, will have organ support days calculated using data from both units.

### Days alive and free of advanced respiratory and renal support within first 28 days

For patients surviving to 28 days following randomisation, the number of days alive and free of advanced respiratory support to day 28 will be defined as the number of calendar days (00:00 to 23:59) on which advanced respiratory support was not received at any time. Patients dying between randomisation and day 28 will be assigned a value of 0. Days alive and free from renal support will be defined in the same way.

### Duration of critical care unit and acute hospital stay

Duration of critical care unit stay will be calculated as the sum of the duration (in fraction of days) from the date and time of randomisation to the date and time of first discharge from critical care or death in critical care , plus the duration of any subsequent admissions to a critical care unit within the same acute hospital stay.

Duration of acute hospital stay will be calculated as the duration (in days) from the date of randomisation to the date of acute hospital discharge or death in acute hospital.

### Cognitive decline at 90 days and one year

Cognitive decline will be assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version)[[12]](#endnote-12), with the total score calculated as the mean of the scores (from 1 to 5) on the sixteen items. Note: one-year data will only be available for a subset of patients recruited up to one year before study closure.

## Clinical analysis methods

The primary outcome of number and percentage of deaths by 90 days following randomisation will be reported. The primary effect estimate will be the absolute risk reduction, reported with a 95% confidence interval. The relative risk will also be reported. Deaths by 90 days following randomisation will be compared between the groups, unadjusted, using Fisher’s exact test. Due to the anticipated low amount of clustering, unadjusted analyses will not take account of site-level effects.

An analysis, adjusted for baseline data, will also be conducted using multilevel logistic regression with a random effect of site. Baseline variables adjusted for in the multilevel logistic regression model will be (all categorical variables are defined and grouped as previously described under baseline characteristics):

* age (linear);
* sex;
* comorbidities;
* dependency prior to admission to acute hospital;
* location prior to admission to critical care and urgency of surgery;
* ICNARC Physiology Score (linear);
* Sepsis-3;
* vasopressors received as a continuous infusion at randomisation; and
* duration of vasopressors prior to randomisation (linear).

Baseline variables were selected for inclusion in the adjusted analysis according to anticipated relationship with outcome. The results of the multilevel logistic regression model will be reported as an adjusted odds ratio with 95% confidence interval. The unadjusted odds ratio will be presented for comparison.

The primary outcome (90-day mortality) will be analysed by the following pre-specified patient subgroups:

* age (linear);
* chronic hypertension (yes, no);
* chronic heart failure (yes, no);
* atherosclerotic disease (yes, no);
* Predicted log-odds of acute hospital mortality from the ICNARC*H*-2015 risk prediction model (linear);
* Sepsis-3; and
* vasopressors received at randomisation(categorised as previously defined).

These analyses will test for an interaction between the subgroup categories (or subgroup variable for linear interactions) and the treatment group in a multilevel logistic regression model, adjusted for the same baseline variables as the primary analysis. For linear interactions, the interaction effect will be illustrated by calculating the adjusted odds ratio within five categories at quintiles of the continuous variable[[13]](#endnote-13).

The primary analysis will be repeated adjusting for adherence to allocated intervention (binary variable, equal to 0 for all patients allocated permissive hypotension with one or more recorded protocol deviation, and 1 for all other patients) using a structural mean model with an instrumental variable of allocated treatment to estimate the complier average causal effect of treatment.[[14]](#endnote-14)

An additional sensitivity analysis will be performed, repeating the primary analysis in the subset of patients who would have been eligible for the trial following the inclusion criteria as defined in the protocol amendment to version 2.0 (i.e. patients restricted to those who had started vasopressors between six and one hours prior to randomisation, and excluding any patients who were receiving only noradrenaline at randomisation at dose levels below 0.1 μg kg−1 min−1).

An exploratory analysis will be performed to investigate difference in the primary outcome between treatment groups, adjusting for treatment intensity at the site level. Before performing this analysis, a number of possible measures of treatment intensity will be assessed using descriptive statistics only - in order to select a clinically meaningful measure for use in the adjusted analysis of outcomes.

Secondary outcomes will be reported by treatment group. Continuous outcomes will be reported using either mean and standard deviations (duration of respiratory support for all patients; duration of renal support for all patients; number of days alive and free of advanced respiratory support to day 28; number of days alive and free of renal support to day 28; IQCODE at 90 days and at 1 year) or median and IQR (duration of advanced respiratory support in patients who received it; duration of renal support in patients who received it; duration of critical care and acute hospital stay). Unadjusted comparisons of continuous outcomes will be made using t-tests or Wilcoxon’s rank sum test (comparisons for duration of stay will be stratified by survival status at discharge). Adjusted comparisons (for all continuous variables excluding duration of stay) will be made using multilevel linear regression – adjusted for the same baseline variables as the adjusted analysis of the primary outcome – using bootstrapping to account for anticipated non-normality in the distribution.[[15]](#endnote-15)

Binary outcomes (mortality at discharge from critical care unit and acute hospital) will be reported using numbers and percentages. Unadjusted comparisons will be made using Fisher’s exact test, and adjusted comparisons using multilevel logistic regression – adjusted for the same baseline variables as the adjusted analysis of the primary outcome.

Time to event outcomes (duration of survival to longest available follow-up) will be reported using Kaplan Meier curves and compared using the log rank test. An adjusted comparison will be performed using a Cox proportional-hazards model adjusted for the same baseline variables as the primary analysis, with shared frailty at the site level.

A subgroup analysis of secondary outcomes will be performed to compare unadjusted and adjusted secondary outcomes in those patients who did/did not have chronic hypertension at baseline.

## Cost-effectiveness analysis

The primary cost-effectiveness outcome is net monetary benefit (NMB) at 90 days following randomisation. The secondary cost-effectiveness outcomes are costs, health-related quality of life (HRQoL), and quality-adjusted life years (QALYs) at 90 days and at one year following randomisation, and NMB at one year following randomisation.

### Cost-effectiveness outcomes at 90 days

A full cost-effectiveness analysis will be undertaken to assess the relative cost-effectiveness of permissive hypotension (MAP target range of 60-65 mmHg) compared to usual care according to the intention-to-treat principle. Resource use and outcome data collected as a part of the 65 trial data will be used to report cost-effectiveness at 90 days by randomised treatment group.

The cost analysis will take a health and personal health services perspective. The primary sources of the resource use data will be the 65 trial case report forms (CRFs), CMP data and individual health service questionnaires on the use of health services which are posted to surviving patients at 90 days and at one year following randomisation. Cost will be calculated from patient-level resource use data on length of stay in critical care and acute hospital, for the index admission and any readmission before six months, use of personal health services after acute hospital discharge and within 90 days post-randomisation, and additional resources required to deliver the intervention. Resource use associated with delivering the intervention will be measured from detailed information collected in the trial CRFs, site visits and expert clinical opinion. A micro-costing method will be applied to record the costs of providing vasopressors within the critical care unit. For each patient, the number of days in critical care will be recorded and assigned to a healthcare resource group (HRG) using mandated data collected for the CCMDS. The cost per hospital bed-day for each HRG category for critical care, and for general medical bed-days will be available from the NHS Payment by Results database. We will report resource use for primary admission and re-admissions. Data on re-admissions will be extracted from the CRFs, the CMP, and from the patient questionnaires. The use of hospital readmission data from three sources (CRFs, CMP and health service questionnaire) is designed to avoid missing hospital episodes (for example not via critical care), but raises the possibility of double-counting (see sensitivity analysis). The frequency of outpatient visits, GP visits and other community care use will be extracted from responses to service use questionnaires. The intervention costs will be aggregated and averaged over patients for each treatment group. Resource use data from the site visits, trial datasets and 90 days questionnaires will be combined with unit costs from the NHS Payment by Results database and from local Trust Finance Departments, to report the total costs per patient at 90 days for both randomised groups.

HRQoL at 90 days will be assessed using the EuroQol EQ-5D-5L questionnaire, with valuation using the EQ-5D-5L value set for England 2018.[[16]](#endnote-16) HRQoL data will be combined with the survival data to report QALYs at 90 days. QALYs will be calculated by valuing each patient’s survival time by their HRQoL at 90 days according to the “area under the curve” approach. For 90-day survivors, QALYs will be calculated using the EQ-5D scores at 90 days, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and 90 days. For decedents between randomisation and 90 days, we will assume zero QALYs.

Net monetary benefits will be calculated by valuing QALY gains at £20,000 per QALY and subtracting incremental costs.

### Cost-effectiveness outcomes at one year

Use of healthcare resources (critical care, general medical length of stay, outpatient and community care) between 90 days and one year will be measured using readmission information from the CMP and follow-up health services questionnaire at one year. Total costs at one year will be estimated by valuing resource with appropriate unit costs.

HRQoL data up to one year will be combined with survival data to report QALYs at one year. For patients surviving up to one year, we will use EQ-5D responses at one year assuming a linear interpolation between the EQ-5D scores at 90 days and one year. For decedents between 90 days and one year, where an EQ-5D score at 90 days is available, a linear interpolation will be applied between the 90-day EQ-5D, and the date of death when a zero EQ-5D score will be applied.

A funding decision means not all patients will be followed up to one year, and so their survival, resource use, and HRQoL data will be censored. Any administrative censoring at one year of resource use, survival and HRQoL will be assumed at random in the base analysis (see below for details of a planned sensitivity analysis to test this assumption).

We will report NMB at one year by valuing QALY gains at one year at £20,000 per QALY and subtracting incremental costs at one year.

### Statistical analysis for cost-effectiveness at 90 days

Differences in cost-effectiveness outcome between the randomised treatment groups will be tested, unadjusted, using the t-test and, adjusted, using multilevel linear regression – adjusted for the same baseline variables as the adjusted analysis of the primary clinical outcome. This analysis will be done once using imputed utility scores for patients with missing data, (see below for details), and then repeated using only patients with non-missing data.

Missing data in costs and EQ-5D score will be handled with multiple imputation, assuming the data are missing at random (MAR) conditional on the observed data. Non-missing will be defined as having all five items completed from the EQ-5D-5L. The cost-effectiveness analysis will use Bivariate Seemingly Unrelated Regression model to allow for correlation between costs and QALYs and multilevel structure of the data. We will calculate the interclass correlation coefficient (ICC) which measures the proportion of the overall variation that occurs at the cluster level[[17]](#endnote-17). If ICC>10% we will use multilevel models (MLM) to handle clustering and avoid potential biases and incorrect inferences. The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 90 days.

The base case analysis will report the incremental effects of randomisation to a permissive hypotension strategy versus usual care. We will report incremental effects as mean differences (95% CI) at a willingness to pay (WTP) of £20,000 per QALY and the probability that the intervention is cost-effective compared to usual care at different levels of WTP. We will also report cost-effectiveness acceptability curves. As outlined below, multiple imputation will be used to address issues posed by missing EQ-5D-5L or cost data (see below for details on methods used to handle missing data).

### Statistical analysis for cost-effectiveness at one year

The statistical analysis of CEA endpoints at one year will follow the same approaches that are outlined for the 90 days endpoint. Censoring of cost, HRQoL and survival data of patients at one year will be assumed at random.

### Sensitivity analysis for cost-effectiveness

#### Sensitivity analyses at 90 days

The following sensitivity analyses will be performed to check the robustness of primary CEA results at 90 days.

1. *HRQoL data*

The three-level version of the EQ-5D descriptive system, the EQ-5D-3L, and the 5L version may result in different cost-effectiveness estimates[[18]](#endnote-18). The sensitivity of the results to the instrument used will be examined using the 3L version. A mapping technique (“crosswalk”) will be used to predict the values of the EQ-5D-3L[[19]](#endnote-19).

We will use Bayesian pattern-mixture models, informed by expert elicitation, to allow departures from MAR for missing EQ-5D-5L values[[20]](#endnote-20). The sensitivity of the results to a full range of diversity of opinion will be examined through a comparison of pooled and individual priors. Posterior probabilities and 95% credible intervals will be reported.

We will explore alternative distributional assumptions for QALYs.

1. *Cost data*

Because of the likely skewed distribution of costs we will consider several distributions that can give a better fit of cost data

 We will assess the implications of potential double-counting of inpatient costs (e.g. costs for vasopressors) across the three sources of resource data.

#### Sensitivity analyses at one year

The above sensitivity analysis will be repeated at one year if there is considerable difference in costs and QALY at one year driven by differences in costs and QALYs between 90 days and one year.

We will test the implications of censoring at random assumptions. Cost and outcomes of patients who are administratively censored for one-year follow-up will be estimated according to their survival probability after the censored period up to one year and observed mean costs and HRQoL of those patients who are alive and not censored[[21]](#endnote-21).

Moreover the CEA results at one year will be used to project lifetime cost-effectiveness results. Lifetime cost-effectiveness will be projected by summarising the relative effects of alternative strategies on long-term survival, and HRQoL as compared with that of age-gender matched general population[[22]](#endnote-22),[[23]](#endnote-23),[[24]](#endnote-24),[[25]](#endnote-25). The survival of the patients who survived up to twelve months post randomisation will be extrapolated over lifetime. The long-term survival of patients will be extrapolated from the maximum available survival data recorded in the trial dataset, by fitting alternative parametric survival curves (e.g. Weibull, exponential, lognormal, log logistic and Gompertz) to the observed survival data. The method of parametric extrapolation of survival will be chosen based on model fit and plausibility when compared with age-gender matched general population survival[[26]](#endnote-26). Survival will then be extrapolated according to chosen parametric function for the duration of years that parametric curves predicts excess mortality compared to age-gender matched general population, after which we will assume that all cause death rates were those of the age-gender matched general population. HRQoL at twelve months will be assumed to apply to each subsequent year of life, after allowing for decrements in HRQoL according to advancing age. We will project lifetime costs by applying morbidity costs estimated at twelve months over the period of excess mortality. Predicted survival and HRQoL will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care.

#### Analysis across subgroups

The results of the cost-effectiveness analysis will be reported at 90 days across subgroups as previously set out for the primary clinical analysis.

# Handling of missing data

The amount of missing clinical primary outcome data is anticipated to be minimal but will be accounted for in a sensitivity analysis. The primary analysis will be repeated once assuming that all patients in the intervention group with missing outcomes survived, and all patients in the usual care group with missing outcomes did not survive. The analysis will then be repeated again with the opposite assumptions. This will then give the absolute range of how much the results could change if the data were complete.

Analysis of cognitive function at 90 days and one year will be done once using patients with non-missing data only (defined as having no more than three missing items from the 16-item IQCODE), and then repeated with missing data imputed among patients known to be alive at those time points, excluding only those who did not consent to access medical records. If necessary, missing data in baseline variables included in the adjusted models will also be imputed.

Multiple imputation will be undertaken using the Multivariate Imputation using Chained Equations (MICE) algorithm, with the model including all baseline variables included in the adjusted models, and all outcome variables. Twenty multiply imputed datasets will be generated. Models will be fitted in each imputed dataset and results combined using Rubin’s rules.

To evaluate the CEA results under the assumption that health-related quality of life are missing not at random (MNAR), i.e. the probability of missing data depends on the patient’s outcome after conditioning on the observed data, a pattern-mixture model approach[[27]](#endnote-27) will be used. Pattern-mixture models allow the outcome to be modelled differently according to whether it is observed or missing. To inform the assumptions about the parameters for the missing pattern that cannot be estimated from the data (sensitivity parameters), expert opinion about EQ-5D-5L differences between patients with missing versus complete data will be elicited from a representative sample of the clinical staff involved with the 65 trial across the different trial centres and other interested experts[[28]](#endnote-28).

# Safety

The numbers of serious adverse events and number and percentage of patients experiencing each serious adverse event following randomisation until critical care discharge will be reported in each treatment group. The total number of patients experiencing one or more serious adverse events will be compared between groups using Fisher’s exact test.

# Statistical software

The analyses will be conducted in Stata/SE version 14.2. Other packages, such as R, may be used for specific analyses.

# Declarations

*Authors’ contributions*

*KT drafted the manuscript which was based on an analysis plan written by AP and revised by KT and ZS. KT will perform the statistical analysis and ZS and AM will perform the health economic analyses. DAH and RG will oversee the statistical and heath economics analyses, respectively. KMR is the director of the Clinical Trials Unit and has oversight of the trial. PM is the chief investigator, FL is the lead clinical investigator and ACG is a trial investigator and contributed towards the writing of the analysis plan. All authors read and approved the final manuscript.*

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*Declaration of Conflicting Interests*

ACG reports that outside of this work he has received speaker fees from Orion Corporation Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare, Bristol-Myers Squibb and GSK, and received grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution. All other authors declare no conflict of interests.

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*Research ethics and patient consent*

This paper represents an analysis plan which was written based on Protocol version 3.1 (dated 20 February 2019) which received favourable ethical opinion from the South Central – Oxford C Research Ethics Committee (REC) (reference: 17/SC/0142) and approval from the Health Research Authority. The full Protocol (including amendments) is available on the NIHR website. The 65 trial was granted an emergency waiver of consent, with patients and/or their Consultee (as appropriate) approached for consent when appropriate following randomisation.

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