Supplement 1 to
Effect of reduced exposure to vasopressors on
90-day mortality in older critically ill patients
with vasodilatory hypotension:
A randomized clinical trial

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This supplement contains the following items:

1. Original protocol, final protocol, summary of changes

2. Original statistical analysis plan, final statistical analysis plan, summary of changes
Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension

STUDY SHORT TITLE
The 65 Trial

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Sponsor representative
Mr Kevin Hunt
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor’s Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: [Signature]

Date: 21/04/2017

Name (please print):

Mr Kevin Hunt

Position:

Chief Executive

Chief Investigator:

Signature: [Signature]

Date: 21/04/2017

Name:

Mr Paul Mouncey

Position:

Senior Researcher
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<td>AE</td>
<td>adverse event</td>
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<tr>
<td>CCMDS</td>
<td>Critical Care Minimum Dataset</td>
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<td>CI</td>
<td>Chief Investigator</td>
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<td>CMP</td>
<td>Case Mix Programme</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<td>CTU</td>
<td>Clinical Trials Unit</td>
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<td>DMEC</td>
<td>Data Monitoring &amp; Ethics Committee</td>
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<td>EQ-5D-5L</td>
<td>European Quality of Life Scale</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<td>Intensive Care National Audit &amp; Research Centre</td>
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<td>INB</td>
<td>Incremental net benefit</td>
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<td>IQCODE</td>
<td>Informant Questionnaire on Cognitive Decline in the Elderly</td>
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<td>MAP</td>
<td>mean arterial pressure</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>National Institute for Health Research</td>
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<td>PI</td>
<td>Principal Investigator</td>
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<td>PIS</td>
<td>Participant Information Sheet</td>
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<td>Patient and Public Involvement</td>
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<td>QALY</td>
<td>Quality-adjusted life year</td>
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<td>RCT</td>
<td>Randomised Clinical Trial</td>
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<td>SAE</td>
<td>serious adverse event</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>TMG</td>
<td>Trial Management Group</td>
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<td>TSC</td>
<td>Trial Steering Committee</td>
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1. Background and rationale

The 65 Trial: Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension

In critically ill patients, hypotension (low blood pressure) is common, especially in patients with severe infections. Raising blood pressure is a complex process involving multiple elements including vasopressors (intravenous drugs), fluids and catheters. Vasopressors (which also stimulate the heart) are mainstays of treatment.

Permissive hypotension refers to the acceptance of blood pressure targets slightly below conventional levels and echoes other permissive therapeutics in the areas of mechanical ventilation (permissive hypoxia(1), permissive hypercapnea(2)) and permissive hypotension in trauma(3).

Current guidelines recommend maintaining mean arterial pressure (MAP – a person’s average blood pressure) above 65 mmHg(4). However, these guidelines are based on low quality evidence and no guidance is given for an upper MAP limit. There is some evidence that overuse of interventions, such as vasopressors, to continue increasing an already high MAP, may be harmful. A recently completed (unpublished) meta-analysis of data from two trials (5, 6) suggests that targeting higher MAP values of between 75 and 85 mmHg, achieved through increased use of intensive interventions, may be associated with an increased risk of death in older critically ill patients.

Doctors and nurses are also faced with the challenging decision of balancing the risks of hypotension against the risks associated with larger doses of vasopressors.

The 65 Trial is testing the hypothesis that the benefits associated with permissive hypotension in older patients will outweigh the risks associated with lower MAP values and medication interventions to raise blood pressure.

1.1 Pilot and feasibility work

Two recently published clinical trials investigating higher versus lower MAP targets for vasopressor treatment suggest the 65 trial is feasible. The OVATION pilot trial(6) was conducted in 120 patients from 11 centres in Canada and the United States. Patient accrual was such that enrolment was capped in the first half of participating centres to allow for site activation in all 11 sites before reaching the overall recruitment target. Despite this active restriction on enrolment, an average of 2.3 patients per centre, per month was achieved. The other trial, SEPSISPAM(5), involved 798 patients, at an enrolment rate of 1.5 patients per centre per month, across 23 participating sites in France.

Even more crucial to the feasibility of both trials was achieving separation in MAP values between the treatment groups (higher and lower MAP targets). In both trials, investigators observed a 10 mmHg difference in the average MAP between arms.
1.2 Efficient design

The 65 Trial was designed to minimize the impact that research can create for critical care unit teams. The trial is nested in an existing network of research-active critical care units participating in the Case Mix Programme (CMP). The CMP, coordinated by the Intensive Care National Audit & Research Centre (ICNARC), is the national clinical audit for adult critical care in England, Wales and Northern Ireland and is a source of high quality, robust and representative data.

The vast majority of data for the 65 Trial will be sourced from the CMP or from NHS Digital via data linkage (e.g. longer-term mortality and subsequent healthcare utilization). Given the importance of protocol adherence and patient safety, primary data collection for the trial will be limited to data related to protocol adherence and adverse event reporting.
2. Aims and objectives

2.1 Aim

The aim of the 65 Trial is to evaluate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) in critically ill patients aged 65 years or over with vasodilatory hypotension.

2.2 Objectives

To estimate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) when compared with usual care.
3. Trial design

The 65 Trial is a pragmatic, multi-centre, parallel group randomised clinical trial (RCT).

3.1 Setting

3.1.1 Trial sites

In this protocol, ‘site’ refers to the 65 NHS adult, general, critical care units where the 65 Trial will be conducted.

3.1.2 Site requirements

- Active participation in the CMP
- Compliance with all responsibilities as stated in the 65 Clinical Trial Site Agreement
- Compliance with all requirements of the trial protocol including the trial treatments and follow-up schedules
- Compliance with the research governance framework for health and social care and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP).

3.1.3 Site responsibilities

- Identify two local Joint-Principal Investigators (PIs) – one critical care consultant and one senior critical care nurse – both of whom will lead the 65 trial locally
- Identify a 65 Research Nurse responsible for day-to-day local trial coordination
- Agree to incorporate the 65 Trial into routine critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations and ensure adherence with the trial protocol
- Agree to randomise all eligible patients and maintain a Screening Log
- Agree to data collection requirements

3.1.4 Site initiation and activation

The following must be in place prior to a site being activated for recruitment:

- a completed site initiation visit
- all relevant institutional approvals (e.g. local confirmation of capacity and capability)
- a fully signed 65 Clinical Trial Site Agreement
- a completed Delegation Log

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation e-mail will be issued to the joint-PIs, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PIs are responsible for ensuring:

- adherence with the most recent approved version of the trial protocol
- training of relevant site staff in accordance with the trial protocol requirements and Good Clinical Practice (GCP) requirements
- appropriate means to identify and randomise eligible patients into the trial
- timely data collection, entry and validation
- prompt notification of all adverse events (as specified in Section 4).

All local staff (i.e. PIs, local investigators, research teams) involved in the conduct of the trial must be listed and signed off on the Delegation Log, once trained, to carry out their delegated duties. The Delegation Log should be copied and sent to the 65 Trial Team at the ICNARC CTU whenever changes are made.

### 3.2 Population

The target patient population for the 65 Trial is critically ill patients aged 65 years and over with vasodilatory hypotension requiring treatment with vasopressor infusion(s).

To be eligible for the 65 Trial, patients must meet all of the inclusion criteria, and none of the exclusion criteria:

#### 3.2.1 Inclusion criteria

- age 65 years or older
- vasodilatory hypotension as assessed by treating clinician
- decision to start vasopressors or started within prior 6 hours following/during adequate fluid resuscitation
- vasopressors expected to continue for 6 hours or more as assessed by treating clinician

#### 3.2.2 Exclusion criteria

- vasopressors being used as therapy for bleeding, ventricular failure (left or right) or post-cardiopulmonary bypass vasoplegia
- ongoing treatment for brain injury or spinal cord injury
- death perceived as imminent
- previous enrolment to the 65 Trial
3.2.3 Co-enrolment

The 65 Trial investigators will consider co-enrolment of 65 Trial participants onto other interventional studies where there is no possible conflict with the 65 Trial objectives. Co-enrolment agreements will be put in place on a case-by-case basis. Co-enrolment will be permitted with studies that do not involve an intervention (e.g. observational studies). Details of any co-enrolment(s) will be documented on the 65 Trial Case Report Form.

3.2.4 Screening

Potentially eligible patients will be screened against the inclusion/exclusion criteria by the local clinical team in the critical care unit, supported by the site research team. Screening Logs will record the reason patients are eligible but are subsequently not enrolled.

3.3 Recruitment and consent

3.3.1 Overview/Rationale

Patients who require vasopressors to treat hypotension in critical care will often need this treatment started in a life-threatening emergency situation. They will therefore most likely lack capacity due to their condition and be unable to provide prior informed consent. They may also be receiving invasive treatments (e.g. mechanical ventilation) and have reduced capacity due to the effects of sedative and analgesic drugs as part of standard care. In such an emergency situation, any delay in commencing treatment could be detrimental to the patient and to the scientific validity of the trial, with the delivery of urgent treatments always the priority of any treating clinical team. This, alongside the potential distress of the emergency situation, makes any attempt to obtain either prior informed consent from the patient, or opinion of their Personal Consultee (i.e. relative or close friend), prior to starting the trial treatment inappropriate.

Considering these reasons, once an eligible patient is identified for the trial (i.e. the patient meets the inclusion criteria and does not meet any exclusion criteria), they will be enrolled and randomised to receive the assigned treatment as soon as possible. This method is known as ‘deferred consent’ or ‘research without prior consent’ and is recognised in European Law. This process will be covered by an emergency waiver of consent under the Mental Capacity Act (approved by South Central - Oxford C Research Ethics Committee (reference: 17/SC/0142)).

N.B. The use of the term ‘deferred’ is a misnomer as a patient will have already received an intervention as part of the trial before any information about the trial is shared with patients and/or consultees. Rather, the process should be understood, first, as the provision of information about what has already happened, and then as an invitation to consent for continued participation and future procedures (where appropriate).
In the rare situation where a patient has been deemed by the treating clinical team to have full capacity and is able to give informed consent at the point of eligibility, they will be approached directly prior to randomisation for verbal consent to take part in the 65 Trial. If they provide verbal consent, they will then be followed up for full written informed consent, in line with the procedures outlined in section 3.3.2.

### 3.3.2 Patient informed deferred consent

Following randomisation, patients will be approached once they have been deemed to have full capacity to provide informed deferred consent. A Participant Information Sheet (PIS) will be provided to the patient. The PIS will provide information about the purpose of the study, what participation means for the patient (e.g. follow-up questionnaires at 90 days and one year – see section 3.6), confidentiality and data security, and the future availability of the trial results.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection. The Consent Form will also cover ongoing data collection and follow-up.

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in the 65 Trial. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient’s medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.

The patient’s General Practitioner will then be sent a letter by the recruiting site to inform them of their patient’s participation in the trial (provided consent has been given for this).

### 3.3.3 Personal Consultee Opinion

Due to the severity of illness and its impact on the mental state of the target population, it will usually not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into the 65 Trial, a delegated member of the site research team will approach the Personal Consultee as soon as appropriate and practically possible to discuss the trial and to seek their opinion as to the patients’ likely wishes and feelings regarding participating in research. Ideally, this
approach would take place within 24-48 hours of randomisation, once the patient’s medical situation is no longer an emergency.

The Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented by information about why the Personal Consultee has been approached at this stage. A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients’ participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in research. Personal Consultees will also be asked to indicate on the Personal Consultee Opinion Form whether, in their opinion, the patient would agree to access to medical records for data collection and receipt of follow-up questionnaires at three months and one year.

Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients’ participation in the 65 Trial. After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the person seeking opinion will invite the Personal Consultee to sign the Personal Consultee Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient’s medical notes and the original kept in the Investigator Site File.

If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in research, then the trial treatment will be stopped and the Personal Consultee asked whether, in their opinion, the patient would be willing to continue with ongoing data collection and/or to be followed-up at three months and one year.

Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.2.2). The patient’s decision will be final, and will supersede the Personal Consultee, where there is disagreement.

### 3.3.4 Nominated Consultee Opinion

In the situation where the patient has died, a Nominated Consultee will be appointed. The Nominated Consultee may be an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust or an independent doctor (i.e. not associated with the conduct of the trial). Opinion of the Nominated Consultee will be sought in the same manner as for the Personal Consultee.

A Nominated Consultee will also be approached in the rare situations where no Personal Consultee is available (or one is available, but unwilling to provide opinion). Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.2.2). The patient’s decision will be final, and will supersede the Nominated Consultee, where there is disagreement.
3.3.5 Discharge prior to consent/opinion being sought

In the rare situation where the patient is discharged from hospital with capacity, then the most appropriate member of the site research team will attempt at least one phone call to the patient within five working days of hospital discharge to inform them of their involvement in the 65 Trial and to provide information about the trial. Following on from the call, as well as if there is no response to the call, the patient will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the PIS and Consent Form (postal version) by post. The letter will direct the patient to the PIS for detailed information on the trial and provide telephone contact details if the patient wishes to discuss the trial with a member of the site research team. The letter will ask the patient to return the Consent Form (postal version) to confirm whether they would like to take part (or not).

If there is no response after four weeks of sending the covering letter, a follow-up letter, alongside second copies of the PIS and Consent Form (postal version), will be sent to the patient. This second letter will provide the same information as the first letter, but will confirm that if no Consent Form is received within four weeks of receipt of the letter, then the participant’s data will be included in the trial unless they notify the site research team otherwise.

If the patient is discharged without capacity, then the opinion of the Personal Consultee will be sought in line with the above process (telephone call then postal approach).

If the participant is transferred to another hospital participating in the 65 trial before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

3.3.6 Refusal or withdrawals of consent/opinion

If patient informed consent is refused or withdrawn, or where consultee opinion indicates that inclusion in the trial would be against the patient’s wishes or best interests, this decision will be respected and abided by, and no further contact made. All data up to the point of this decision will be retained in the trial, unless the patient or consultee requests otherwise.

3.3.7 Randomisation

Randomisation will be performed as soon as possible after confirming eligibility. Patients will be randomised following a 1:1 sequence to either the intervention group (permissive hypotension) or usual care using a dedicated telephone or web-based randomisation service available 24 hours/seven days per week. In addition, during the recruitment period a member of the 65 trial team will be available 24 hours/seven days per week to address emergency recruitment, randomisation or clinical issues that arise.
Allocation will be by randomised permuted blocks (with variable block lengths of 4, 6 and 8), stratified by recruiting site. As this is a large trial, the risk of chance imbalance in prognostic factors is low and the need to randomise patients during a very short time-frame mandates that the randomisation process is as simple as possible. For these reasons, we have elected not to stratify the randomisation process on additional potential confounders.

Following enrolment in the 65 Trial, each participant will be assigned a unique 65 Trial number and a Case Report Form (CRF) will be completed by the local team.

### 3.4 Procedures

#### 3.4.1 Intervention

Permissive hypotension - MAP target range of 60 - 65 mmHg whilst receiving vasopressors

The decision to discontinue vasopressors will depend on the patients' ability to maintain the MAP target stipulated by the protocol without vasopressors. Clinical teams will be actively reminded to consider discontinuing vasopressor therapy if the patients are able to maintain MAP values of at least 60 mmHg. The trial treatment will apply at any point the patient requires vasopressors during their admission in the critical care unit.

All other usual care will be provided at the discretion of the treating clinical team, as per local practice.

#### 3.4.2 Control

Patients in the control arm will receive usual care (as per local practices).

#### 3.4.3 Co-interventions

The selection of specific vasopressor agents (norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin, metaraminol), use of inotropes, fluids and corticosteroids will be recorded but left to the discretion of the treating team.

As per usual care of patients receiving vasopressors, central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) will be usually be in place.
3.5 Outcomes

**Primary outcome - Clinical effectiveness:**
- all-cause mortality at 90 days

**Primary outcome – Cost-effectiveness:**
- incremental net monetary benefit (INB), evaluated at the NICE recommended threshold of £20,000 per quality-adjusted life year (QALY), at 90 days

**Secondary outcomes:**
- mortality at discharge from the critical care unit and acute hospital
- duration of survival to longest available follow-up
- duration of advanced respiratory and renal support (defined according to the Critical Care Minimum Dataset [CCMDS]) during the critical care unit stay
- days alive and free of advanced respiratory support and renal support
- duration of critical care unit and acute hospital stay
- cognitive function assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version) at 90 days and one year
- health-related quality of life, assessed using the EuroQol EQ-5D-5L questionnaire, at 90 days and one year
- resource use and costs at 90 days and one year
- estimated lifetime incremental cost-effectiveness

3.6 Data collection

To maximise the efficiency of the trial design, data collection for the 65 Trial is nested in the CMP. Data from the CMP to be used in the trial analysis will include:
- baseline demographics and risk factors, including predicted risk of death from recently developed and validated risk prediction models for acute hospital and longer-term mortality
- secondary outcomes of critical care unit and acute hospital mortality, organ support (calendar days of organ support in critical care for the CCMDS), duration of critical care unit and acute hospital stay

All patients recruited to the trial will be asked to provide consent for data linkage with other routine data sources. Data obtained from routine data sources (e.g. NHS Digital) will include:
- date of death for deaths occurring after discharge from acute hospital, by data linkage with death registrations, until longest available follow-up (e.g. patients recruited in the first month of the trial will be able to be followed-up for survival until 24 months)
- hospital costs for subsequent hospitalisations, by data linkage with Hospital Episode Statistics
- critical care costs, based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.
Additional data items collected at each site specifically for the trial will be limited to:

- patient and personal consultee details (to enable questionnaire follow-up at 90 days and one year)
- confirmation of eligibility criteria and consent/opinion
- data to monitor adherence with the protocol and separation in MAP values and vasopressor dose/duration between the trial groups
- data related to the use of intravenous fluids, inotropes and corticosteroids
- adverse event reporting.

### 3.7 Questionnaire follow-up

Each participant will be followed up with a questionnaire up to a maximum of one year (the primary outcome will be captured at 90 days through data linkage (as outlined in section 3.6)).

Survival status at 90 days and at one year will also be obtained via data-linkage with nationally held records. At each time-point, survivors will be posted a questionnaire by the ICNARC CTU containing the EQ-5D-5L, IQCODE (short version) and health services questionnaire. The questionnaires are designed to take no longer than 15 minutes to complete and patients will be provided with a pen and self-addressed stamped envelope for ease of return. Only patients recruited during the first nine months of the recruitment period will be contacted at one year.

Non-responders will be telephoned three weeks after the questionnaire was posted, and asked to check whether they have received the questionnaire. If preferable for the patient, they will be offered the option of either being sent another copy of the questionnaire in the post, completing the questionnaire over the telephone with a trained member of the 65 Trial team, or to receive the questionnaire in a preferred alternative format (e.g. email).

If a patient is an in-patient at a participating site at either of the follow-up time-points, the site research team will be asked to approach the patient and conduct the questionnaire with them in hospital, if willing and if their condition permits.

If a patient is on their initial acute hospital admission at either of the follow-up time points, they will not be asked to complete the health services questionnaire, as this contains only questions that are relevant following discharge from acute hospital.

### 3.8 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper CRFs will be available to the sites. The site PIs will oversee and be responsible for data collection, quality and recording. Collection of data
can be delegated (as per the Delegation Log) by the site PIs to qualified members of the research team.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution.

Security of the electronic data entry system is maintained through user names and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act. ICNARC is registered under the Data Protection Act (Registration number: Z6289325).

3.9 Monitoring

3.9.1 Central monitoring

The trial team at the ICNARC CTU will communicate regularly with sites via email, telephone, teleconferences and newsletters. This will include central review of consent forms and essential documents. Data relating to adherence with the protocol will be actively and regularly reviewed centrally and local PIs will be contacted regularly to ensure adherence and the quality of the data.

3.9.2 Site monitoring

The site monitoring plan will follow a risk-based strategy, including an assessment of the sites and local research teams (e.g. experience of multicentre research, RCTs, etc.). Sites will be visited to monitor and discuss adherence to the trial protocol and standard operating procedures. Following all site visits, a report will be sent to the site summarising the visit, documents reviewed and any relevant observations. This process will inform constant improvements to Standard Operating Procedures (SOPs) required to ensure clarity and consistency across sites.
4. Safety monitoring

4.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

**Adverse Event**

An adverse event is described as any untoward medical occurrence or effect in a patient participating in a study, which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavourable symptom or disease temporally associated with the use of the study treatment, whether or not it is related to the allocated study treatment.

**Serious Adverse Event**

An adverse event is defined as serious if it:

- results in death
- is life-threatening
- requires significant in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

Life threatening, in the definition of a Serious Adverse Event (adverse events), refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

**Unexpected and Related Serious Adverse Event**

A suspected adverse event related to the treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

4.2 Severity

- **None**: indicates no event or complication
- **Mild**: complications result in only temporary harm and do not require clinical treatment
4.3 Relatedness

- **None**: there is no evidence of any relationship to the study treatment
- **Unlikely**: there is little evidence to suggest a relationship to the study treatment, and there is another reasonable explanation of the event
- **Possibly**: there is some evidence to suggest a relationship to the study treatment, although the influence of other factors may have contributed to the event
- **Probably**: there is probable evidence to suggest a relationship to the study treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a relationship to the study treatment, and other possible contributing factors can be ruled out.

4.4 Expectedness

- **Expected**: the event is listed as an expected AE in Appendix 2
- **Unexpected**: the event is not listed as an expected AE in Appendix 2.

4.5 Recording and reporting procedures

It is important to consider the natural history of the critical illness affecting each patient enrolled, the expected complications of this illness and the relevance of the complications to the trial treatment (7). All patients eligible for the 65 Trial are critically ill, and due to the complexity of their condition are at increased risk of experiencing multiple adverse events. Consequently, the labelling of a Serious Adverse Event should be limited to serious events, yet which might reasonably occur as a consequence of the trial intervention (i.e. not events that are part of the natural history of the primary disease process or expected complications of critical illness). Adverse events must be reported in the participant’s medical notes, on the 65 Trial CRF and to the ICNARC CTU using the 65 Trial adverse events Reporting Form, by fax or using the web-based electronic case report form, within 24 hours of observing or learning of the adverse event(s). All sections of the adverse events Reporting Form must be completed.
All other adverse events that occur between randomisation and 30 days post-randomisation must be recorded in the participant’s medical notes and on the 65 Trial CRF. Information regarding date and time of event onset, severity and relatedness of the adverse events to study treatment must be recorded.

The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1.

4.6 Follow-up of serious adverse events

All adverse events must be followed-up until resolution. The site PIs or other delegated investigator(s) must provide follow-up adverse events report(s) if the adverse event(s) has not been resolved at the time of the initial report submission.

4.7 Central processing of serious adverse event reports

On receipt of the SAE report, a member of the 65 Trial Management Group will evaluate the event for relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is judged unexpected and potentially related to the trial intervention, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Lead Investigators, Trial Management Group, Trial Steering Committee and Data Monitoring and Ethics Committee and REC for review on a regular basis (as deemed necessary).

4.8 Additional safety monitoring

The ICNARC CTU will also monitor data for any trial related events that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in adverse events, the Trial Management Group will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the ICNARC CTU will inform the REC, as appropriate.

4.9 Notifying the Research Ethics Committee

Adverse events that do not require expedited reporting will be reported in the annual progress report which will be submitted by the ICNARC CTU to the REC. This will commence one year from the date of approval for the trial.
Figure 1 Adverse event recording and reporting

- Adverse Event
  - Is the event on the list of expected AEs?
    - NO
      - Clearly related to the patient's medical condition or standard treatment?*
        - NO
          - Does not meet SAE definition
            - Assess severity
              - Record on CRF
        - YES
          - Meets SAE definition
            - Complete SAE Reporting Form
              - Notify ICNARC CTU within 24 hours either by fax (020 7831 6879) or using the web-based case report form
            - No further action required, however the event should be recorded in the patient’s medical notes, and followed up by site research staff

*If there is any uncertainty about whether the AE is associated with study treatment, then it should be reported.
5. Trial closure

5.1 End of trial

The end of the trial will be when all patients recruited in the first nine months of the recruitment period have completed their one year follow-up, at which point the ‘Declaration of end of trial’ form will be submitted to the REC by the ICNARC CTU.

5.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all centrally held trial-related documents for a minimum of five years, in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The site PIs will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of five years after the end of the study. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other applicable regulatory requirements.

Guidance on archiving will be provided in the study-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

5.3 Early discontinuation of the trial

The number of interim analyses will be limited to detect early evidence of harm and irrefutable mortality differences. A single interim analysis will be carried out after the recruitment and follow-up of 500 patients using a Peto-Haybittle stopping rule (P<0.001) to recommend early termination due to either effectiveness or harm. Further interim analyses will be performed if requested by the Data Monitoring and Ethics Committee.
6. Statistics and data analysis

6.1 Sample size calculation

Assuming 90-day mortality of 35% within usual clinical care (based on CMP data for patients aged 65 years or older admitted to critical care and receiving advanced cardiovascular support), a sample size of 1402 patients will provide 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 will aim to recruit a total of 1440 patients.

Based on the anticipated recruitment rate of 1.5 patients per site per month, recruitment will be completed by 65 sites recruiting for approximately 18 months (accounting for staggered activation of participating sites).

6.2 Statistical analysis

6.2.1 Feasibility stage

A feasibility analysis will be conducted on patients recruited during the first six months (as per the grant timeline). The anticipated sample size at this point will provide 90% power to detect as statistically significant (P<0.05) a separation of 4 mg (norepinephrine equivalent) in mean total vasopressor dose, assuming a standard deviation of 15 mg in each group, and a separation of 5 mmHg in peak MAP while receiving vasopressors, assuming a standard deviation of 7.5 mmHg in each group.

The secondary feasibility objectives will be to assess the ability to open sites, and screen and recruit patients. The following additional progression criteria will be required:

1. A minimum of 50 sites are open to recruitment; and
2. The recruitment rate in open sites is at least 80% of anticipated.

6.2.2 Clinical effectiveness analysis

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. All analyses will be performed according to the intention-to-treat principle. Results will be reported in accordance with the CONSORT statement.

Analysis of dichotomous outcomes will be performed both unadjusted (using Fisher’s exact test) and adjusted for baseline covariates (using multilevel logistic regression with unit-level random effects). Analyses of time-to-event data (time to death) will be performed by Kaplan-Meier methods and Cox proportional hazards modelling. Analyses of days alive and free of respiratory and/or renal support will be performed by bootstrapped t-tests to account for non-normality. Analyses of duration of critical care unit and acute hospital stay will be performed by Wilcoxon rank-sum tests, stratified by
survival status. Analyses of cognitive and physical function and health-related quality of life will be performed by t-tests and adjusted linear regression. Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the pre-specified baseline covariates.

6.2.3 Health economic evaluation

A full cost-effectiveness analysis will be undertaken to assess the relative cost-effectiveness of the intervention versus usual care. Resource use and outcome data collected as part of the trial will be used to report the relative cost-effectiveness at 90 days, according to the incremental net benefit, and to also project the lifetime cost-effectiveness.

The cost analysis will use detailed, micro-costing methods to record the costs of providing vasopressors within the critical care unit. This approach will enable the cost analysis to recognise any cost variation across different patient subgroups. Each patient’s critical care unit admission will be assigned to the appropriate Healthcare Resource Group (HRG) using mandated data 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.

The cost analysis will take a health and personal health services perspective. Information on subsequent critical care unit and hospital admissions and emergency department and outpatient attendances will be obtained via data linkage between the trial data and the CMP and Hospital Episode Statistics. Use of primary care and community health services will be assessed by questionnaires at 90 days and one year and valued using unit costs taken from published sources. Data from the EQ-5D-5L questionnaires at 90 days and one year post-randomisation will be combined with survival data to report quality adjusted life year (QALYs).

The cost-effectiveness analysis will report the mean (95% confidence interval) incremental costs and QALYs of the intervention versus usual care at 90 days, incremental net benefit (INB) at a willingness to pay of £20,000 per QALY, and the probability that the intervention is cost-effective compared with usual care at different levels of willingness to pay for a QALY gained. The cost-effectiveness analysis will use regression methods to report relative cost-effectiveness according to pre-defined subgroups, and will be combined with multiple imputation to address issues posed by missing EQ-5D-5L or cost data. Survival analysis will be used to extrapolate any within-trial differences in costs and QALYs in projecting lifetime cost-effectiveness.

Sensitivity analyses will test whether the results are robust to methodological assumptions.
7. Trial management and oversight

The Chief Investigator (Mr Paul Mouncey) and the Lead Clinical Investigator (Dr Francois Lamontagne) will take overall responsibility for delivery of the 65 Trial and oversee progress against timelines/milestones.

7.1 Good research practice

The 65 Trial will be sponsored by ICNARC and managed by the ICNARC CTU according to the Medical Research Council’s Good Research Practice: Principles and Guidelines and Scientific Misconduct Policy and Procedure(8), based on the principles of the International Conference on Harmonization guidelines on Good Clinical Practice and the Department of Health’s Research Governance Framework for Health and Social Care. ICNARC policies and procedures are based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

7.2 Trial Management Group (TMG)

The TMG comprises the 65 Trial Investigators (listed on page 5) – led by the two lead investigators (Mr Paul Mouncey and Dr Francois Lamontagne). The day-to-day trial team will comprise the two Lead Investigators, Clinical Trials Unit co-investigators (Professor Kathy Rowan and Dr David Harrison) alongside the Trial Manager (Mr Alvin Richards-Belle), Trial Statistician (Ms Zohra Zenasni) and Data Manager (Mr Nick Hudson). Quarterly meetings of the TMG will be held to ensure effective communication. In addition, the day-to-day trial team will meet regularly to discuss the progress of the trial and findings from other related research.

7.3 Trial Steering Committee (TSC)

A TSC will be established in line with the latest NIHR HTA guidelines (i.e. consist of 75% independent members – including the Chair). The Trial Steering Committee will be responsible for overall supervision on behalf of the Sponsor and Funder, and will ensure that it is conducted in accordance with the rigorous standards set out in the Department of Health’s Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The Trial Steering Committee will comprise the Lead Investigators (PM, FL) plus independent members (including independent patient and public involvement (PPI) representatives). Representatives of the Sponsor and Funder will be invited to observe at TSC meetings, which will take place at the start and after the feasibility stage, and at any other time determined by the independent Chair.
7.4 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be set-up to monitor recruitment and retention, adherence with the intervention and patient safety. Meetings will take place immediately prior to TSC meetings.

8. Ethical compliance

The 65 Trial will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as the ICNARC CTU research policies and procedures.

8.1 Trial registration

This trial has been registered with the ISRCTN Registry (ISRCTN10580502).

8.2 Central ethical compliance

The trial has received a favourable ethical opinion from the South Central - Oxford C Research Ethics Committee (Reference: 17/SC/0142) and approval from the Health Research Authority. The ICNARC CTU will submit annual progress reports and all amendments to the 65 protocol to the REC for review. The ICNARC CTU will provide relevant approved trial documents and other related materials to participating sites.

8.3 Local ethical compliance

It is the responsibility of the site Joint-PIs to obtain the necessary local approvals for 65, including confirmation of capacity and capability. Evidence of confirmation of capacity and capability at each participating site must be provided to the ICNARC CTU prior to site activation (see section 3.1).

8.4 Patient and Public Involvement (PPI)

There are two PPI representatives as co-investigators on the 65 Trial and who have been involved in its development. As members of the TMG, they are fully involved in the work planned as part of this trial. In addition, independent PPI representative(s) will be sought for membership of the TSC.
8.5 Data protection and participant confidentiality

Identifiable patient data, including full name, contact details, date of birth and NHS number will be required by the ICNARC CTU to successfully follow-up participants. The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored securely.

We will also seek consent to share the patients' anonymised data or to be contacted by the study team for future research.

All data will be securely stored in a locked cabinet or in an encrypted electronic file. ICNARC will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act (1998).

8.6 Declaration of interests

All trial investigators have confirmed that they do not have any financial or other conflicts of interest to declare in relation to this trial.

8.7 Access to the final study dataset

Once the data from the study are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.
9. Sponsorship and funding

9.1 Sponsorship and indemnity

ICNARC is the Sponsor for the 65 Trial and holds professional indemnity insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

9.2 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: 15/80/39).
10. Dissemination

The results of the 65 Trial will be widely and actively disseminated. The results of the 65 Trial will be presented at: regional critical care network meetings; national professional conferences; the ICNARC Case Mix Programme Annual Conference; the Annual Meeting of the UK Critical Care Research Forum; and national and international critical care conferences/meetings.

A Study Report to the NIHR HTA programme will present a detailed description of the project and the results along with recommendations for future policy, practice and research. Articles will be prepared for publication in peer-reviewed scientific journals, as well as in relevant professional journals.

10.1 Knowledge mobilization

If targeting a lower MAP value is found to be clinically and cost-effective, implementation of the trial outputs into clinical guidelines and subsequently dissemination into the NHS will occur.
11. References

## Appendix 1 – Protocol version history

<table>
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<tr>
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<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of changes made</th>
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<td>N/A</td>
<td>1.1</td>
<td>21 April 2017</td>
<td>Alvin Richards-Belle</td>
<td>• Section 3.3 (Recruitment and consent) refined</td>
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<td></td>
<td></td>
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Appendix 2 - Expected adverse events

Expected AEs that could be observed in participants up to 30 days following randomisation:

- supraventricular cardiac arrhythmia
- ventricular cardiac arrhythmia
- myocardial infarction
- extremity necrosis
- mesenteric ischaemia
- severe acute renal failure

[This list is not exhaustive. If an AE, as defined in Section 4, occurs this should be recorded and reported as described in Section 4.5]
Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension

STUDY SHORT TITLE
The 65 Trial

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number: 15/80/39). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA Programme, NIHR, NHS or the Department of Health.
Research reference numbers

Protocol version number and date
V3.1, 20 February 2019

IRAS Number
215503

REC Number
17/SC/0142

NIHR Portfolio CPMS ID
34223

ISRCTN Registry Number
ISRCTN10580502

Sponsor name and reference
Intensive Care National Audit & Research Centre (ICNARC) (reference: 01/05/17)

Funder name and reference
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project number: 15/80/39)

Chief Investigator
Mr Paul Mouncey

Sponsor representative
Ms Kerrie Gemmill
Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor’s Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:
Signature: 

Date: 

20 February 2019

Name (please print):
Ms Kerrie Gemmill
Position:
Managing Director

Chief Investigator:
Signature: 

Date: 

20 February 2019

Name:
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Position:
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<td>LSHTM</td>
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Abbreviations

AE  adverse event               
ARR  absolute risk reduction    
CCMDS  Critical Care Minimum Dataset  
CI  Chief Investigator           
CMP  Case Mix Programme         
CRF  Case Report Form           
CTU  Clinical Trials Unit       
DMEC  Data Monitoring & Ethics Committee  
EQ-5D-5L  European Quality of Life Scale  
GCP  Good Clinical Practice     
HTA  Health Technology Assessment  
ICH  International Conference on Harmonisation  
ICNARC  Intensive Care National Audit & Research Centre  
INB  Incremental net benefit    
IQCODE  Informant Questionnaire on Cognitive Decline in the Elderly   
MAP  mean arterial pressure     
NHS  National Health Service    
NIHR  National Institute for Health Research   
PI  Principal Investigator       
PIS  Participant Information Sheet 
PPI  Patient and Public Involvement  
QALY  Quality-adjusted life year  
RCT  Randomised Clinical Trial   
REC  Research Ethics Committee  
RRR  relative risk reduction    
SAE  serious adverse event      
SOP  Standard Operating Procedure 
TMG  Trial Management Group     
TSC  Trial Steering Committee
1. Background and rationale

The 65 Trial: Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension

In critically ill patients, hypotension (low blood pressure) is common, especially in patients with severe infections. Raising blood pressure is a complex process involving multiple elements including vasopressors (intravenous drugs), fluids and catheters. Vasopressors (which also stimulate the heart) are mainstays of treatment.

Permissive hypotension refers to the acceptance of blood pressure targets slightly below conventional levels and echoes other permissive therapeutics in the areas of mechanical ventilation (permissive hypoxia\(^1\), permissive hypercapnea\(^2\)) and permissive hypotension in trauma\(^3\).

Current guidelines recommend maintaining mean arterial pressure (MAP – a person’s average blood pressure) above 65 mmHg\(^4\). However, these guidelines are based on low quality evidence and no guidance is given for an upper MAP limit. There is some evidence that overuse of interventions, such as vasopressors, to continue increasing an already high MAP, may be harmful. A recently completed meta-analysis\(^5\) of data from two trials\(^6,7\) suggests that targeting higher MAP values of between 75 and 85 mmHg, achieved through increased use of intensive interventions, may be associated with an increased risk of death in older critically ill patients.

Doctors and nurses are also faced with the challenging decision of balancing the risks of hypotension against the risks associated with larger doses of vasopressors.

The 65 Trial is testing the hypothesis that the benefits associated with permissive hypotension in older patients will outweigh the risks associated with lower MAP values and medical interventions to raise blood pressure.

1.1 Pilot and feasibility work

Two recently published clinical trials investigating higher versus lower MAP targets for vasopressor treatment suggest the 65 trial is feasible. The OVATION pilot trial\(^7\) was conducted in 120 patients from 11 centres across Canada and the United States. Patient accrual was such that enrolment was capped in the first half of participating centres to allow for site activation in all 11 sites before reaching the overall recruitment target. Despite this active restriction on enrolment, an average of 2.3 patients per centre, per month was achieved. The other trial, SEPSISPAM\(^6\), involved 798 patients, at an enrolment rate of 1.5 patients per centre, per month, across 23 participating sites in France.

Even more crucial to the feasibility of both trials was achieving separation in MAP values between the treatment groups (higher and lower MAP targets). In both trials, investigators observed a 10 mmHg difference in the average MAP between arms.
1.2 Efficient design

The 65 Trial was designed to minimize the impact that research can create for critical care unit teams. The trial is nested in an existing network of research-active critical care units participating in the Case Mix Programme (CMP). The CMP, coordinated by the Intensive Care National Audit & Research Centre (ICNARC), is the national clinical audit for adult critical care in England, Wales and Northern Ireland and is a source of high quality, robust and representative data.

The vast majority of data for the 65 Trial will be sourced from the CMP or from NHS Digital via data linkage (e.g. longer-term mortality and subsequent healthcare utilization). Given the importance of protocol adherence and patient safety, primary data collection for the trial will be limited to data related to protocol adherence and adverse event reporting.
2. Aims and objectives

2.1 Aim

The aim of the 65 Trial is to evaluate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) in critically ill patients aged 65 years or over with vasodilatory hypotension.

2.2 Objectives

To estimate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) when compared with usual care.
3. Trial design

The 65 Trial is a pragmatic, multi-centre, parallel group randomised clinical trial (RCT).

3.1 Setting

3.1.1 Trial sites

In this protocol, ‘site’ refers to the 65 NHS adult, general, critical care units where the 65 Trial will be conducted.

3.1.2 Site requirements

- Active participation in the CMP
- Compliance with all responsibilities as stated in the 65 Clinical Trial Site Agreement
- Compliance with all requirements of the trial protocol including the trial treatments and follow-up schedules
- Compliance with the research governance framework for health and social care and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP).

3.1.3 Site responsibilities

- Identify two local Joint-Principal Investigators (PIs) – one critical care consultant and one senior critical care nurse – both of whom will lead the 65 Trial locally
- Identify a 65 Research Nurse responsible for day-to-day local trial coordination
- Agree to incorporate the 65 Trial into routine critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations and ensure adherence with the trial protocol
- Agree to randomise all eligible patients and maintain a Screening Log
- Agree to data collection requirements.

3.1.4 Site initiation and activation

The following must be in place prior to a site being activated for recruitment:

- a completed site initiation visit
- all relevant institutional approvals (e.g. local confirmation of capacity and capability)
- a fully signed 65 Clinical Trial Site Agreement
- a completed Delegation Log

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation e-mail will be issued to the joint-PIs, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PIs are responsible for ensuring:

- adherence with the most recent approved version of the trial protocol
- training of relevant site staff in accordance with the trial protocol and Good Clinical Practice (GCP) requirements
- appropriate means to identify and randomise eligible patients into the trial
- timely data collection, entry and validation
- prompt notification of all adverse events (as specified in Section 4).

All local staff (i.e. PIs, local investigators, research teams) involved in the conduct of the trial must be listed and signed off on the Delegation Log, once trained, to carry out their delegated duties. The Delegation Log should be copied and sent to the 65 Trial Team at the ICNARC CTU whenever changes are made.

### 3.2 Population

The target patient population for the 65 Trial is critically ill patients aged 65 years and over with vasodilatory hypotension requiring treatment with vasopressor infusion(s).

To be eligible for the 65 Trial, patients must meet all of the inclusion criteria, and none of the exclusion criteria:

#### 3.2.1 Inclusion criteria

- age 65 years or older
- vasodilatory hypotension as assessed by treating clinician
- started infusion* of vasopressors within prior 6 hours (if noradrenaline, then a minimum dose of 0.1 $\mu$g kg$^{-1}$ min$^{-1}$)
- adequate fluid resuscitation is completed or ongoing
- vasopressors expected to continue for 6 hours or more as assessed by treating clinician

*for at least one hour

#### 3.2.2 Exclusion criteria

- vasopressors being used solely as therapy for bleeding, acute ventricular failure (left or right) or post-cardiopulmonary bypass vasoplegia
- ongoing treatment for brain injury or spinal cord injury
3.2.3 Co-enrolment

The 65 Trial investigators will consider co-enrolment of 65 Trial participants onto other interventional studies where there is no possible conflict with the 65 Trial objectives. Co-enrolment agreements will be put in place on a case-by-case basis. Co-enrolment will be permitted with studies that do not involve an intervention (e.g. observational studies). Details of any co-enrolment(s) will be documented on the 65 Trial Case Report Form (CRF).

3.2.4 Screening

Potentially eligible patients admitted (or accepted for admission) to the participating adult, general, critical care unit will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Screening Logs will record the reason patients are eligible but are subsequently not enrolled.

3.3 Recruitment and consent

3.3.1 Overview/Rationale

Patients who require vasopressors to treat hypotension in critical care will often need this treatment started in a life-threatening emergency situation. They will therefore most likely lack capacity due to their condition and be unable to provide prior informed consent. They may also be receiving invasive treatments (e.g. mechanical ventilation) and have reduced capacity due to the effects of sedative and analgesic drugs as part of standard care. In such an emergency situation, any delay in commencing treatment could be detrimental to the patient and to the scientific validity of the trial, with the delivery of urgent treatments always the priority of any treating clinical team. This, alongside the potential distress of the emergency situation, makes any attempt to obtain either prior informed consent from the patient, or opinion of their Personal Consultee (i.e. relative or close friend), prior to starting the trial treatment inappropriate.

Considering these reasons, once an eligible patient is identified for the trial (i.e. the patient meets the inclusion criteria and does not meet any exclusion criteria), they will be enrolled and randomised to receive the assigned treatment as soon as possible. This method is known as ‘deferred consent’ or ‘research without prior consent’ and is recognised in European Law. This process will be covered by an emergency waiver of consent under the Mental Capacity Act (approved by South Central - Oxford C Research Ethics Committee (reference: 17/SC/0142)).
N.B. The use of the term ‘deferred’ is a misnomer as a patient will have already received an intervention as part of the trial before any information about the trial is shared with patients and/or consultees. Rather, the process should be understood, first, as the provision of information about what has already happened, and then as an invitation to consent for continued participation and future procedures (where appropriate).

In the rare situation where a patient has been deemed by the treating clinical team to have full capacity and is able to give informed consent at the point of eligibility, they will be approached directly prior to randomisation for verbal consent to take part in the 65 Trial. If they provide verbal consent, they will then be followed up for full written informed consent, in line with the procedures outlined in section 3.3.2.

3.3.2 Patient informed deferred consent

Following randomisation, patients will be approached once they have been deemed to have full capacity to provide informed deferred consent. A Participant Information Sheet (PIS) will be provided to the patient. The PIS will provide information about the purpose of the study, what participation means for the patient (e.g. follow-up questionnaires at 90 days and one year – see section 3.6), confidentiality and data security, and the future availability of the trial results.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection. The Consent Form will also cover ongoing data collection and follow-up.

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in the 65 Trial. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient’s medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.

The patient’s General Practitioner will then be sent a letter by the recruiting site to inform them of their patient’s participation in the trial (provided consent has been given for this).

3.3.3 Personal Consultee Opinion

Due to the severity of illness and its impact on the mental state of the target population, it will usually not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.
In the interim, once notified of the enrolment of a patient into the 65 Trial, a delegated member of the site research team will approach the Personal Consultee as soon as appropriate and practically possible to discuss the trial and to seek their opinion as to the patients’ likely wishes and feelings regarding participating in research. Ideally, this approach would take place within 24-48 hours of randomisation, once the patient’s medical situation is no longer an emergency.

The Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented by information about why the Personal Consultee has been approached at this stage. A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients’ participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in research. Personal Consultees will also be asked to indicate on the Personal Consultee Opinion Form whether, in their opinion, the patient would agree to access to medical records for data collection and receipt of follow-up questionnaires at three months and one year.

Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients’ participation in the 65 Trial. After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the person seeking opinion will invite the Personal Consultee to sign the Personal Consultee Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient’s medical notes and the original kept in the Investigator Site File.

If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in research, then the trial treatment will be stopped and the Personal Consultee asked whether, in their opinion, the patient would be willing to continue with ongoing data collection and/or to be followed-up at three months and one year.

Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.3.2). The patient’s decision will be final, and will supersede the Personal Consultee, where there is disagreement.

3.3.4 Nominated Consultee Opinion

In the situation where the patient has died, a Nominated Consultee will be appointed. The Nominated Consultee may include an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust or an independent doctor (i.e. not associated with the conduct of the trial). Opinion of the Nominated Consultee will be sought in the same manner as for the Personal Consultee.

A Nominated Consultee will also be approached in the rare situations where no Personal Consultee is available (or one is available, but unwilling to provide opinion). Upon patient
recovery, the patient will be approached directly for informed deferred consent (see section 3.3.2). The patient’s decision will be final, and will supersede the Nominated Consultee, where there is disagreement.

3.3.5 Discharge prior to consent/opinion being sought

In the rare situation where the patient is discharged from hospital with capacity prior to consent/opinion being sought, then the most appropriate member of the site research team will attempt at least one phone call to the patient within five working days of hospital discharge to inform them of their involvement in the 65 Trial and to provide information about the trial. Following on from the call, as well as if there is no response to the call, the patient will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the PIS and Consent Form (postal version) by post. The letter will direct the patient to the PIS for detailed information on the trial and provide telephone contact details if the patient wishes to discuss the trial with a member of the site research team. The letter will ask the patient to return the Consent Form (postal version) to confirm whether they would like to take part (or not).

If there is no response after four weeks of sending the covering letter, a follow-up letter, alongside second copies of the PIS and Consent Form (postal version), will be sent to the patient. This second letter will provide the same information as the first letter, but will confirm that if no Consent Form is received within four weeks of the letter being sent, then the participant’s data will be included in the trial unless they notify the site research team otherwise.

If the patient is discharged without capacity, then the opinion of the Personal Consultee will be sought in line with the above process (telephone call then postal approach).

If the participant is transferred to another hospital participating in the 65 trial before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

3.3.6 Refusal or withdrawals of consent/opinion

If patient informed consent is refused or withdrawn, or where consultee opinion indicates that inclusion in the trial would be against the patient’s wishes or best interests, this decision will be respected and abided by, and no further contact made. All data up to the point of this decision will be retained in the trial, unless the patient or consultee requests otherwise.

3.3.7 Randomisation

Randomisation will be performed as soon as possible after confirming eligibility. Patients will be randomised following a 1:1 sequence to either the intervention group (permissive hypotension) or usual care using a dedicated telephone or web-based randomisation
service available 24 hours/seven days per week. In addition, during the recruitment period a member of the 65 Trial team will be available 24 hours/seven days per week to address emergency recruitment, randomisation or clinical issues that arise.

Allocation will be by randomised permuted blocks (with variable block lengths), stratified by recruiting site. As this is a large trial, the risk of chance imbalance in prognostic factors is low and the need to randomise patients during a very short time-frame mandates that the randomisation process is as simple as possible. For these reasons, we have elected not to stratify the randomisation process on additional potential confounders.

Following enrolment in the 65 Trial, each participant will be assigned a unique 65 Trial number and a CRF will be completed by the local team.

3.4 Procedures

3.4.1 Intervention

Patients in the intervention group will be treated using the permissive hypotension strategy – a MAP target range of 60 - 65 mmHg whilst receiving vasopressors.

The decision to discontinue vasopressors will depend on the patients' ability to maintain the MAP target stipulated by the protocol without vasopressors. Clinical teams will be actively reminded to consider discontinuing vasopressor therapy if the patients are able to maintain MAP values of at least 60 mmHg. The trial treatment will apply at any point the patient requires vasopressors during their admission in the critical care unit.

All other usual care will be provided at the discretion of the treating clinical team, as per local practice.

If a patient develops exclusion criteria (see section 3.2.2.) after randomisation, it will be at the discretion of the treating clinical team as to whether the MAP target is continued, with patient safety guiding this decision.

3.4.2 Control

Patients in the control arm will receive usual care (as per local practices).

3.4.3 Co-interventions

The selection of specific vasopressor agents (norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin, metaraminol, terlipressin), use of inotropes, fluids and corticosteroids will be recorded but left to the discretion of the treating team.
As per usual care of patients receiving vasopressors, central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) will be usually be in place.

3.5 Outcomes

Primary outcome - Clinical effectiveness:
- all-cause mortality at 90 days

Primary outcome – Cost-effectiveness:
- incremental net monetary benefit (INB), evaluated at the NICE recommended threshold of £20,000 per quality-adjusted life year (QALY), at 90 days

Secondary outcomes:
- mortality at discharge from the critical care unit and acute hospital
- duration of survival to longest available follow-up
- duration of advanced respiratory and renal support (defined according to the Critical Care Minimum Dataset [CCMDS]) during the critical care unit stay
- days alive and free of advanced respiratory support and renal support
- duration of critical care unit and acute hospital stay
- cognitive function assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version) at 90 days and one year
- health-related quality of life, assessed using the EuroQol EQ-5D-5L questionnaire, at 90 days and one year
- resource use and costs at 90 days and one year
- estimated lifetime incremental cost-effectiveness

3.6 Data collection

To maximise the efficiency of the trial design, data collection for the 65 Trial is nested in the CMP. Data from the CMP to be used in the trial analysis will include:
- baseline demographics and risk factors, including predicted risk of death from recently developed and validated risk prediction models for acute hospital and longer-term mortality
- secondary outcomes of critical care unit and acute hospital mortality, organ support (calendar days of organ support in critical care for the CCMDS), duration of critical care unit and acute hospital stay

All patients recruited to the trial will be asked to provide consent for data linkage with other routine data sources. Data obtained from routine data sources (e.g. NHS Digital) will include:
- date of death for deaths occurring after discharge from acute hospital, by data linkage with death registrations, until longest available follow-up (e.g. patients
recruited in the first month of the trial will be able to be followed-up for survival until 24 months)
- hospital costs for subsequent hospitalisations, by data linkage with Hospital Episode Statistics
- critical care costs, based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.

Additional data items collected at each site specifically for the trial will be limited to:
- patient and personal consultee details (to enable questionnaire follow-up at 90 days and one year)
- confirmation of eligibility criteria and consent/opinion
- data to monitor adherence with the protocol and separation in MAP values and vasopressor dose/duration between the trial groups
- data related to the use of intravenous fluids, inotropes and corticosteroids
- adverse event reporting.

3.7 Questionnaire follow-up

Each participant will be followed up with a questionnaire up to a maximum of one year (the primary outcome will be captured at 90 days through data linkage (as outlined in section 3.6)).

Survival status at 90 days and at one year will also be obtained via data-linkage with nationally held records. At each time-point, survivors will be posted a questionnaire by the ICNARC CTU containing the EQ-5D-5L, IQCODE (short version) and health services questionnaire. The questionnaires are designed to take no longer than 15 minutes to complete and patients will be provided with a pen and self-addressed stamped envelope for ease of return. Only patients recruited during the first fourteen months of the recruitment period will be contacted at one year.

Non-responders will be telephoned three weeks after the questionnaire was posted, and asked to check whether they have received the questionnaire. If preferable for the patient, they will be offered the option of either being sent another copy of the questionnaire in the post, completing the questionnaire over the telephone with a trained member of the 65 Trial team, or to receive the questionnaire in a preferred alternative format (e.g. email).

If a patient is an in-patient at a participating site at either of the follow-up time-points, the site research team will be asked to approach the patient and conduct the questionnaire with them in hospital, if willing and if their condition permits.

If a patient is on their initial acute hospital admission at either of the follow-up time points, they will not be asked to complete the health services questionnaire, as this contains only questions that are relevant following discharge from acute hospital.
3.8 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper CRFs will be available to the sites. The site PIs will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PIs to qualified members of the research team.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution.

Security of the electronic data entry system is maintained through user names and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act. ICNARC is registered under the Data Protection Act (Registration number: Z6289325).

3.9 Monitoring

3.9.1 Central monitoring

The trial team at the ICNARC CTU will communicate regularly with sites via email, telephone, teleconferences and newsletters. This will include central review of consent forms and essential documents. Data relating to adherence with the protocol will be actively and regularly reviewed centrally and local PIs will be contacted regularly to ensure adherence and the quality of the data.

3.9.2 Site monitoring

The site monitoring plan will follow a risk-based strategy, including an assessment of the sites and local research teams (e.g. experience of multicentre research, RCTs, etc.). Sites will be visited to monitor and discuss adherence to the trial protocol and standard operating procedures. Following all site visits, a report will be sent to the site summarising the visit, documents reviewed and any relevant observations. This process will inform constant improvements to Standard Operating Procedures (SOPs) required to ensure clarity and consistency across sites.
4. Safety monitoring

4.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

Adverse Event

An adverse event is described as any untoward medical occurrence or effect in a patient participating in a study, which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavourable symptom or disease temporally associated with the use of the study treatment, whether or not it is related to the allocated study treatment.

Serious Adverse Event

An adverse event is defined as serious if it:

- results in death
- is life-threatening
- requires in-patient hospitalisation or significant prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

Life threatening, in the definition of a Serious Adverse Event, refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Unexpected and Related Serious Adverse Event

A suspected adverse event related to the treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

4.2 Severity

- **None**: indicates no event or complication
- **Mild**: complications result in only temporary harm and do not require clinical treatment
• **Moderate**: complications require clinical treatment but do not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitations to the patient

• **Severe**: complications require clinical treatment and results in significant prolongation of hospital stay and/or permanent functional limitation

• **Life threatening**: complications may lead to death

• **Fatal**: indicates that the patient died as a direct result of the complication/adverse events.

### 4.3 Relatedness

- **None**: there is no evidence of any relationship to the study treatment
- **Unlikely**: there is little evidence to suggest a relationship to the study treatment, and there is another reasonable explanation of the event
- **Possibly**: there is some evidence to suggest a relationship to the study treatment, although the influence of other factors may have contributed to the event
- **Probably**: there is probable evidence to suggest a relationship to the study treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a relationship to the study treatment, and other possible contributing factors can be ruled out.

### 4.4 Expectedness

- **Expected**: the event is listed as an expected AE in Appendix 2
- **Unexpected**: the event is not listed as an expected AE in Appendix 2.

### 4.5 Recording and reporting procedures

It is important to consider the natural history of the critical illness affecting each patient enrolled, the expected complications of this illness and the relevance of the complications to the trial treatment. All patients eligible for the 65 Trial are critically ill, and due to the complexity of their condition are at increased risk of experiencing multiple adverse events. Consequently, the labelling of a Serious Adverse Event (SAE) should be limited to serious events, yet which might reasonably occur as a consequence of the trial treatment (i.e. not events that are part of the natural history of the primary disease process or expected complications of critical illness). SAEs must be reported in the participant’s medical notes, on the 65 Trial CRF, and reported to the ICNARC CTU using the 65 Trial SAE Reporting Form, by fax or using the web-based electronic CRF, within 24 hours of observing or learning of the SAE(s). All sections of the SAE Reporting Form must be completed.
All other adverse events that occur between randomisation and critical care unit discharge must be recorded in the participant’s medical notes and on the 65 Trial CRF. Information regarding date and time of event onset, severity and relatedness of the adverse events to study treatment must be recorded.

The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1.

4.6 Follow-up of serious adverse events

All adverse events must be followed-up until resolution. The site PIs or other delegated investigator(s) must provide follow-up adverse events report(s) if the adverse event(s) has not been resolved at the time of the initial report submission.

4.7 Central processing of Serious Adverse Event reports

On receipt of the SAE report, a clinical member of the 65 Trial Management Group will evaluate the event for relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is judged unexpected and potentially related to the trial intervention, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Lead Investigators, Trial Management Group, Trial Steering Committee and Data Monitoring and Ethics Committee and REC for review on a regular basis (as deemed necessary).

4.8 Additional safety monitoring

The ICNARC CTU will also monitor data for any trial related events that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in adverse events, the Trial Management Group will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the ICNARC CTU will inform the REC, as appropriate.

4.9 Notifying the Research Ethics Committee

Adverse events that do not require expedited reporting will be reported in the annual progress report which will be submitted by the ICNARC CTU to the REC. This will commence one year from the date of approval for the trial.
Figure 1 Adverse event recording and reporting

1. **Adverse Event**
   - Is the event on the list of expected AEs?
     - **YES**
       - Meets SAE definition
         - Complete SAE Reporting Form
           - Notify ICNARC CTU within 24 hours either by fax (020 7831 6879) or using the web-based case report form
     - **NO**
       - Record on CRF
         - Assess relatedness
         - Assess severity
   - **NO**
     - Does not meet SAE definition
       - **NO**
         - Record on CRF
       - **YES**
         - Clearly related to the patient’s medical condition or standard treatment?*
           - **YES**
             - No further action required, however the event should be recorded in the patient’s medical notes, and followed up by site research staff
           - **NO**
             - Does not meet SAE definition

*If there is any uncertainty about whether the AE is associated with study treatment, then it should be reported.
5. Trial closure

5.1 End of trial

The end of the trial will be when all participants have completed their 90-day follow-up, at which point the ‘Declaration of end of trial’ form will be submitted to the REC by the ICNARC CTU.

5.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all centrally held trial-related documents for a minimum of five years, in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The site PIs will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of five years after the end of the study. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other applicable regulatory requirements.

Guidance on archiving will be provided to sites in the study-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

5.3 Early discontinuation of the trial

The number of interim analyses will be limited to detect early evidence of harm and irrefutable mortality differences. A single interim analysis will be carried out after the recruitment and follow-up of 500 patients using a Peto-Haybittle stopping rule (P<0.001) to recommend early termination due to either effectiveness or harm. Further interim analyses will be performed if requested by the Data Monitoring and Ethics Committee (DMEC).
6. Statistics and data analysis

6.1 Sample size calculation

Assuming 90-day mortality of 35% within usual care (control group - based on CMP data for patients aged 65 years or older admitted to critical care and receiving advanced cardiovascular support) and a 2.5% withdrawal/loss to follow-up rate; a sample size of 2,600 patients (1,300 per group) will provide 90% power to detect as statistically significant (P<0.05) a 6% absolute risk reduction (ARR) – corresponding to a 17% relative risk reduction (RRR) – to 29% in the intervention group.

If the pre-trial assumption regarding the control group event rate is incorrect, this sample size will retain at least 85% power to detect the specified ARR (and smaller RRR) even if the mortality is as high as 50% and at least 80% power to detect the specified RRR (and smaller ARR) if the mortality is as low as 29%.

It is anticipated that recruitment will be completed by 65 sites recruiting for approximately 21 months (accounting for staggered activation of participating sites).

6.2 Statistical analysis

6.2.1 Feasibility stage

A feasibility analysis will be conducted on patients recruited during the first six months (as per the grant timeline). The anticipated sample size at this point will provide 99% power to detect as statistically significant (P<0.05) the pre-specified clinically important separation between groups both of 10 mg (norepinephrine equivalent) in mean total vasopressor dose, assuming a standard deviation of 15 mg in each group, and/or a separation of 5 mmHg in peak MAP while receiving vasopressors, assuming a standard deviation of 7.5 mmHg in each group.

The secondary feasibility objectives will be to assess the ability to open sites, and screen and recruit patients. The following additional progression criteria will be required:

1. A minimum of 50 sites are open to recruitment; and
2. The recruitment rate in open sites is at least 80% of anticipated.

6.2.2 Clinical effectiveness analysis

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. All analyses will be performed according to the intention-to-treat principle. Results will be reported in accordance with the CONSORT statement.
Analysis of dichotomous outcomes will be performed both unadjusted (using Fisher’s exact test) and adjusted for baseline covariates (using multilevel logistic regression with unit-level random effects). Analyses of time-to-event data (time to death) will be performed by Kaplan-Meier methods and Cox proportional hazards modelling. Analyses of days alive and free of respiratory and/or renal support will be performed by bootstrapped t-tests to account for non-normality. Analyses of duration of critical care unit and acute hospital stay will be performed by Wilcoxon rank-sum tests, stratified by survival status. Analyses of cognitive and physical function and health-related quality of life will be performed by t-tests and adjusted linear regression. Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the pre-specified baseline covariates.

6.2.3 Health economic evaluation

A full cost-effectiveness analysis will be undertaken to assess the relative cost-effectiveness of the intervention versus usual care. Resource use and outcome data collected as part of the trial will be used to report the relative cost-effectiveness at 90 days, according to the incremental net benefit, and to also project the lifetime cost-effectiveness.

The cost analysis will use detailed, micro-costing methods to record the costs of providing vasopressors within the critical care unit. This approach will enable the cost analysis to recognise any cost variation across different patient subgroups. Each patient’s critical care unit admission will be assigned to the appropriate Healthcare Resource Group (HRG) using mandated data 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.

The cost analysis will take a health and personal health services perspective. Information on subsequent critical care unit and hospital admissions and emergency department and outpatient attendances will be obtained via data linkage between the trial data and the CMP and Hospital Episode Statistics. Use of primary care and community health services will be assessed by questionnaires at 90 days and one year and valued using unit costs taken from published sources. Data from the EQ-5D-5L questionnaires at 90 days and one year post-randomisation will be combined with survival data to report quality adjusted life year (QALYs).

The cost-effectiveness analysis will report the mean (95% confidence interval) incremental costs and QALYs of the intervention versus usual care at 90 days, incremental net benefit (INB) at a willingness to pay of £20,000 per QALY, and the probability that the intervention is cost-effective compared with usual care at different levels of willingness to pay for a QALY gained. The cost-effectiveness analysis will use regression methods to report relative cost-effectiveness according to pre-defined subgroups, and will be combined with multiple imputation to address issues posed by missing EQ-5D-5L or cost data. Survival analysis will be used to extrapolate any within-trial differences in costs and QALYs in projecting lifetime cost-effectiveness.
Sensitivity analyses will test whether the results are robust to methodological assumptions.

7. Trial management and oversight

The Chief Investigator (Mr Paul Mouncey) and the Lead Clinical Investigator (Dr Francois Lamontagne) will take overall responsibility for delivery of the 65 Trial and oversee progress against timelines/milestones.

7.1 Good research practice

The 65 Trial will be sponsored by ICNARC and managed by the ICNARC CTU according to the Medical Research Council’s Good Research Practice: Principles and Guidelines and Scientific Misconduct Policy and Procedure, based on the principles of the International Conference on Harmonization guidelines on Good Clinical Practice and the Department of Health’s Policy Framework for Health and Social Care Research. ICNARC policies and procedures are based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

7.2 Trial Management Group (TMG)

The TMG comprises the 65 Trial Investigators (listed on page 5) – led by the two lead investigators (Mr Paul Mouncey and Dr Francois Lamontagne). The day-to-day trial team will comprise the two Lead Investigators, Clinical Trials Unit co-investigators (Professor Kathy Rowan and Dr David Harrison) alongside the Trial Manager (Mr Alvin Richards-Belle), Trial Statistician (Mrs Karen Thomas) and Data Manager (Mr Nick Hudson). Quarterly meetings of the TMG will be held to ensure effective communication. In addition, the day-to-day trial team will meet regularly to discuss the progress of the trial and findings from other related research.

7.3 Trial Steering Committee (TSC)

A TSC will be established in line with the latest NIHR HTA guidelines (i.e. consist of 75% independent members – including the Chair). The Trial Steering Committee will be responsible for overall supervision on behalf of the Sponsor and Funder, and will ensure that it is conducted in accordance with the rigorous standards set out in the Department of Health’s Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The Trial Steering Committee will comprise the Lead Investigators (PM, FL) plus independent members (including independent patient and public involvement (PPI) representatives). Representatives of the Sponsor and
Funder will be invited to observe at TSC meetings, which will take place at the start and after the feasibility stage, and at any other time determined by the independent Chair.

7.4 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be set-up to monitor recruitment and retention, adherence with the intervention and patient safety. Meetings will take place immediately prior to TSC meetings.

8. Ethical compliance

The 65 Trial will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the UK Data Protection Act, the Mental Capacity Act, as well as the ICNARC CTU research policies and procedures.

8.1 Trial registration

This trial has been registered with the ISRCTN Registry (ISRCTN10580502).

8.2 Central ethical compliance

The trial has received a favourable ethical opinion from the South Central - Oxford C Research Ethics Committee (Reference: 17/SC/0142) and approval from the Health Research Authority. The ICNARC CTU will submit annual progress reports and all amendments to the 65 protocol to the REC for review. The ICNARC CTU will provide relevant approved trial documents and other related materials to participating sites.

8.3 Local ethical compliance

It is the responsibility of the site Joint-PIs to obtain the necessary local approvals for 65, including confirmation of capacity and capability. Evidence of confirmation of capacity and capability at each participating site must be provided to the ICNARC CTU prior to site activation (see section 3.1).

8.4 Patient and Public Involvement (PPI)

There are two PPI representatives as co-investigators on the 65 Trial and who have been involved in its development. As members of the TMG, they are fully involved in the work planned as part of this trial. In addition, independent PPI representative(s) will be sought for membership of the TSC.
8.5 Data protection and participant confidentiality

Identifiable patient data, including full name, contact details, date of birth and NHS number will be required by the ICNARC CTU to successfully follow-up participants. The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored securely.

We will also seek consent to share the patients' anonymised data or to be contacted by the study team for future research.

All data will be securely stored in a locked cabinet or in an encrypted electronic file. ICNARC will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.6 Declaration of interests

All trial investigators have confirmed that they do not have any financial or other conflicts of interest to declare in relation to this trial.

8.7 Access to the final study dataset

Once the data from the study are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.
9. Sponsorship and funding

9.1 Sponsorship and indemnity

ICNARC is the Sponsor for the 65 Trial and holds professional indemnity insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

9.2 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: 15/80/39).

Full title of the funded project: Evaluating the clinical and cost effectiveness of using a more conservative mean arterial pressure target range to guide careful titration of vasopressors to minimise dose and duration in older critically ill patients with vasodilatory hypotension: the 65 trial.
10. Dissemination

The results of the 65 Trial will be widely and actively disseminated. The results of the 65 Trial will be presented at: regional critical care network meetings; national professional conferences; the ICNARC Case Mix Programme Annual Conference; the Annual Meeting of the UK Critical Care Research Forum; and national and international critical care conferences/meetings.

A Study Report to the NIHR HTA programme will present a detailed description of the project and the results along with recommendations for future policy, practice and research. Articles will be prepared for publication in peer-reviewed scientific journals, as well as in relevant professional journals.

10.1 Knowledge mobilisation

If targeting a lower MAP value is found to be clinically and cost-effective, implementation of the trial outputs into clinical guidelines and subsequently dissemination into the NHS will occur.
11. References


# Appendix 1 – Protocol version history

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<td>• Section 4.7 (Questionnaire follow-up) updated</td>
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Appendix 2 - Expected adverse events

Expected AEs that could be observed in participants up to critical care discharge following randomisation:

- supraventricular cardiac arrhythmia
- ventricular cardiac arrhythmia
- myocardial infarction
- extremity necrosis
- mesenteric ischaemia
- severe acute renal failure

[This list is not exhaustive. If an AE, as defined in Section 4, occurs this should be recorded and reported as described in Section 4.5]
Trial Protocol summary of changes

Protocol v1.1, 21 April 2017
Original approved protocol

Protocol v1.2, 23 May 2017

1) Typographical error in the internal pilot phase progression criteria amended – increase the required separation between groups to from 4mg to 10 mg (norepinephrine equivalent).

2) Clarification added to the delivery of the intervention to account for situations where a patient develops an exclusion criteria post-randomisation.

3) Minor typographical and administrative changes.

Protocol v2.0, 29 November 2017

1) With agreement of the Trial Steering Committee, refinement of the inclusion criteria to specify that participants must have already commenced on a vasopressor infusion prior to randomisation and, if receiving norepinephrine, a minimum dose of at least 0.1 μg kg⁻¹ min⁻¹ was required

2) Correction to the procedure for recording and reporting of serious adverse events.

3) Minor administrative changes.

Protocol v3.0, 19 March 2018

1) Revision of the sample size calculation to detect a smaller absolute risk reduction in 90-day mortality (from 8% to 6%), requiring a sample size of 2,600 patients (from 1,440 patients).

During the internal feasibility assessment, reviewed by the Trial Steering Committee (TSC) in January 2018, it was noted that the duration of vasopressor therapy in the control group (usual care) was lower than initially anticipated. The TSC therefore strongly recommended that the trial team consider re-powering the trial to detect a smaller difference. The National Institute for Health Research – Health Technology Assessment Programme approved additional site funding to enable delivery of this increase in sample size.

Protocol v3.1, 20 February 2019

1) Correction to the definition of ‘End of Trial’
Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension: The 65 Trial

Statistical Analysis Plan, Version 1.0, 28 February 2018

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This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number: 15/80/39). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA Programme, NIHR, NHS or the Department of Health.
Roles and responsibilities

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<td>Author: Mr Akshay Patel</td>
<td><img src="image1" alt="Signature" /></td>
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<tr>
<td>Statistical Research Assistant, ICNARC</td>
<td></td>
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<tr>
<td>Senior Statistician: Professor David Harrison</td>
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<tr>
<td>Head Statistician, ICNARC</td>
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<td>Chief Investigator: Mr Paul Mouncey</td>
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<td>Head of Research, ICNARC</td>
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<td>Lead Clinical Investigator: Dr François Lamontagne</td>
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<tr>
<td>Associate Professor, Université de Sherbrooke, Quebec, Canada</td>
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Version history

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1. Introduction

1.1 Background and rationale
In critically ill patients, hypotension (low blood pressure) is common, especially in patients with severe infections. Raising blood pressure is a complex process involving multiple elements including vasopressors (intravenous drugs), fluids and catheters. Vasopressors, which increase the cardiac workload, are mainstays of treatment.

Permissive hypotension refers to the acceptance of blood pressure targets slightly below conventional levels and echoes other permissive therapeutics in the areas of mechanical ventilation (permissive hypoxia, permissive hypercapnia) and permissive hypotension in trauma.¹

Current guidelines recommend maintaining a mean arterial pressure (MAP) of at least 65 mmHg. However, these guidelines are based on low quality evidence and no guidance is given for an upper MAP limit. There is some evidence that overuse of vasopressors may be harmful, especially in older patients who are more vulnerable to iatrogenic complications in general. A recently completed individual patient data meta-analysis of data from two trials suggests that targeting higher MAP values of between 75 and 85 mmHg, achieved through increased use of intensive interventions, may be associated with an increased risk of death in older critically ill patients.²

In the context of this emerging evidence, doctors and nurses are faced with the challenge of balancing the risks of hypotension against the risks associated with larger doses of vasopressors.

The 65 Trial is testing the hypothesis that the benefits associated with permissive hypotension (and reduced exposure to vasopressors) in older patients will outweigh the risks associated with lower MAP values.

This document describes the proposed statistical analyses for the 65 Trial. It is important to set these out and to agree them in advance of inspecting the outcome data for the trial, so that data-derived decisions in the analyses are avoided.³ This statistical analysis plan has been prepared in accordance with recent published guidelines.⁴ Cost and cost-effectiveness analyses will be documented separately.

1.2 Aim
The aim of the 65 Trial is to evaluate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) in critically ill patients aged 65 years or over with vasodilatory hypotension.

1.3 Objectives
To estimate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) when compared with usual care.
2. Study Methods

2.1 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 (MAP target range 60-65 mmHg whilst receiving vasopressors) or usual care.

2.2 Randomisation
Patients are randomised using a dedicated telephone or web-based randomisation service available 24 hours/seven days per week. Allocation is by randomised permuted blocks (with variable block lengths), stratified by recruiting site. As this is a large trial, the risk of chance imbalance in prognostic factors is low and the need to randomise patients during a very short time-frame mandates that the randomisation process is as simple as possible. For these reasons, we elected not to stratify the randomisation process on additional potential confounders.

2.3 Sample size
Assuming 90-day mortality of 35% within usual clinical care (based on Case Mix Programme data for patients aged 65 years or older admitted to critical care and receiving advanced cardiovascular support), a sample size of 1402 patients will provide 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 will aim to recruit a total of 1440 patients.

2.4 Framework
All outcomes will be tested for superiority.

2.5 Statistical interim analyses and stopping guidance
An internal feasibility assessment was conducted after the first six months of the trial recruitment period against the following progression criteria:

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

The internal feasibility assessment was successfully completed and all progression criteria were met.

A single interim analysis of 90-day mortality will be 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 will be conducted using a Peto-Haybittle stopping rule (P < 0.001) to guide recommendations for early termination due to either effectiveness or harm. Further interim analyses would be performed only if requested by the DMEC. The Trial Statistician, Senior Statistician and DMEC will not be blinded to treatment allocation. All other investigators will remain unaware of the results of the interim analysis, other than the recommendation of the DMEC to continue or to terminate recruitment.
2.6 Timing of final analysis
The end of the trial will be when all patients recruited in the first nine months of the recruitment period have completed their one-year follow-up. Following the end of the Trial, any patients remaining in follow-up will be censored, the trial database will be locked and the final analysis conducted.

2.7 Timing of outcome assessments
The timings of all outcomes assessments are taken relative to the date of randomisation. Patients surviving to 90 days and one year will be followed up with a questionnaire.
3. Statistical Principles

3.1 Confidence intervals and P values
All statistical tests 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 subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects.⁵,⁶

3.2 Adherence and protocol deviations

3.2.1 Exposure
Exposure to the intervention will be assessed by the following parameters, calculated for each treatment group:

- Mean arterial pressure – mean (SD) and median (IQR) of the (1) highest and (2) mean MAP for each patient whilst receiving vasopressors, and difference in means with 95% confidence interval
- Duration of vasopressor therapy – mean (SD) and median (IQR) of the total duration (hours) from the later of the 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 comes first), and difference in means with 95% confidence interval
- Receipt of vasopressors – the number and percentage of patients receiving each vasopressor (norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin, metaraminol, terlipressin)
- Total dose of vasopressors – the median (IQR) among patients receiving the relevant vasopressor(s) and mean (SD) among all patients (including those not receiving the vasopressor(s) with a value of 0) of the total dose (mg) of vasopressors for (1) norepinephrine, epinephrine, dopamine, phenylephrine and vasopressin combined, expressed as norepinephrine equivalent (see below), (2) metaraminol, and (3) terlipressin, and difference in means with 95% confidence interval
- Dose-rate of vasopressor infusion – mean (SD) and median (IQR) of the (1) highest and (2) mean rate of norepinephrine equivalents (µg kg⁻¹ min⁻¹) and metaraminol (mg h⁻¹), and difference in means with 95% confidence interval

The distribution across patients of the daily values of the following parameters in each group will be presented in the form of box and whisker plots for days 1-7 following randomisation among all patients receiving vasopressors on that day:

- Mean arterial pressure – (1) highest and (2) mean MAP for each patient whilst receiving vasopressors
- Dose-rate of vasopressor infusion – (1) highest and (2) mean rate of norepinephrine equivalents (µg kg⁻¹ min⁻¹) and metaraminol (mg h⁻¹)

The numbers of patients included on each day will be reported at the foot of the figure.
Norepinephrine equivalents will be calculated using the following conversion:

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3.2.2 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 (65 mmHg) in the permissive hypotension group defines a protocol deviation (i.e. there can be no protocol deviation in the usual care group). Potential protocol deviations, identified from the trial data, will trigger a query to the participating site who will have the possibility 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 recordings), the Trial Management Group may determine that the event did not constitute a protocol deviation.

We will report the number and percentage of patients with at least one protocol deviation in the permissive hypotension group. Adherence will be defined at the patient level as not having experienced any protocol deviations.

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

4.1 Screening data
All participating sites have been asked to keep a Screening Log of all patients accepted for admission to the critical care unit, aged 65 years or older and receiving vasopressors – including those who are randomised, and those who are not. The following summaries will be presented:

- Total number of days screening, calculated as the sum of the number of days screening at each site
- Number of screened patients
- Number of eligible patients (% of screened patients)
- Number of recruited patients (% of eligible patients) and reasons for non-recruitment, where known

The recruitment rate per site per month, defined as number of recruited patients/(total number of days screening×12/365), will be calculated both overall (reported with 95% confidence interval, assuming a Poisson distribution) and by site and summarised across sites by the median (IQR).

4.2 Eligibility
The eligibility criteria are as follows.

Inclusion criteria:

- Age 65 years or older
- Vasodilatory hypotension as assessed by treating clinician
- Started infusion* of vasopressors within prior 6 hours (if noradrenaline, then a minimum dose of 0.1 μg kg⁻¹ min⁻¹)
- Adequate fluid resuscitation is completed or ongoing
- Vasopressors expected to continue for 6 hours or more as assessed by treating clinician

*for at least one hour

Exclusion criteria:

- Vasopressors being used solely as therapy for bleeding, acute ventricular failure (left or right) or post-cardiopulmonary bypass vasoplegia
- Ongoing treatment for brain injury or spinal cord injury
- Death perceived as imminent
- Previous enrolment to the 65 Trial

Among those screened (aged 65 years or older and receiving vasopressors), 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 6 hours or more, and (3) meeting each of the exclusion criteria will be reported.

4.3 Recruitment
A CONSORT flow diagram⁷ 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
• excluded from the primary analysis (with reasons)

4.4 Withdrawal/follow-up
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:
  o whether a consultee (personal or nominated) was approached; or
  o whether the patient regained capacity prior to a consultee being approached
• For those where a consultee was approached
  o 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
  o whether the patient regained capacity before hospital discharge
• For those that regained capacity:
  o 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

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.

The number and percentage of patients lost to follow-up for mortality (as a percentage of all randomised patients) and for questionnaire outcomes (as a percentage of survivors) at 90 days and one year will be reported in each group. The baseline characteristics (as described in Section 4.5) of patients completing a follow-up questionnaire at each time point will be compared with those of patients known to be alive at that time point that did not complete a follow-up questionnaire. The disposition of patients at 90 days and one year will be reported in each group for those returning completed questionnaires.

4.5 Baseline patient characteristics
The following baseline demographic and clinical data will be summarised for each treatment group but not subjected to statistical testing:

• Demographics
  o Age – mean (SD)
  o Sex (male, female) – number (%)
• Comorbidities – number (%)
  o Chronic hypertension (yes, no)
  o Chronic heart disease (yes, no)
  o Atherosclerotic disease (yes, no)
- End-stage renal failure (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) – number (%)
- 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) – number (%)
- Acute severity of illness from first 24 hours following admission to the unit
  - APACHE II Score – mean (SD)
  - ICNARC Physiology Score – mean (SD)
  - ICNARC 2015 model predicted risk of death – median (IQR)
  - Sepsis-3 (no sepsis, sepsis, septic shock) – number (%)
- Mean arterial pressure (mmHg) at randomisation – mean (SD)
- Vasopressor infusions received at randomisation – number (%)
  - None*
  - Norepinephrine < 0.1 μg kg⁻¹ min⁻¹†
  - Norepinephrine ≥ 0.1 μg kg⁻¹ min⁻¹
  - Metaraminol
  - Other/combination (details in footnote)
- Duration of vasopressor infusion prior to randomisation (minutes) – median (IQR)

*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
5. Analysis

5.1 Outcome definitions

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

5.1.2 Secondary outcomes

5.1.2.1 Mortality at discharge from the critical care unit and acute hospital
Mortality at discharge from the critical care unit will be 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 leave acute hospital.

5.1.2.2 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.

5.1.2.3 Duration of advanced respiratory and renal support during the critical care unit stay
Advanced respiratory support and renal support will be defined according to the UK Department of Health Critical Care Minimum Dataset (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 outside of the critical care unit will be assumed to be free of organ support.

5.1.2.4 Days alive and free of advanced respiratory and renal support
For patients surviving to 28 days following randomisation, the number of days alive and free of advanced respiratory and renal support to day 28 will be defined as the number of calendar days (00:00 to 23:59) on which neither advanced respiratory support nor renal support was not received at any time. Patients dying between randomisation and day 28 will be assigned a value of 0.

5.1.2.5 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 days) from the date and time of randomisation (for the critical care admission during which the patient was randomised) or the date and time of admission to the critical care unit (for any subsequent admissions) to the date and time of discharge from the critical care unit or death in the critical care unit for all admissions to critical care during the 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.

5.1.2.6 Cognitive function at 90 days and one year
Cognitive function will be assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version), with the total score calculated as the mean of the scores (from 1 to 5) on the sixteen items.

5.1.2.7 Health-related quality of life at 90 days and one year
Health-related quality of life will be assessed using the EuroQol EQ-5D-5L questionnaire, with valuation using the EQ-5D-5L value set for England 2018.
5.2 Analysis methods

5.2.1 Primary outcome
The 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:

- Age (linear)
- Sex (binary- male, female)
- Comorbidities (binary covariates for each of: chronic hypertension, chronic heart disease, atherosclerotic disease, end-stage renal failure)
- Dependency prior to admission to acute hospital (categorical- able to live without assistance with 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 (categorical- ED/not in hospital, theatre-elective/scheduled surgery, theatre-emergency/urgent surgery, other critical care unit, ward or intermediate care area)
- ICNARC Physiology Score (linear)
- Sepsis-3 (no sepsis, sepsis, septic shock)
- Vasopressor infusions received at randomisation (categorical- none or norepinephrine < 0.1 \( \mu \text{g kg}^{-1} \text{min}^{-1} \), norepinephrine \( \geq 0.1 \mu \text{g kg}^{-1} \text{min}^{-1} \), metaraminol, other/combination)
- Duration of vasopressor infusion 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 patient subgroups:

- Age (linear)
- Chronic hypertension (yes, no)
- Chronic heart disease (yes, no)
- Atherosclerotic disease (yes, no)
- End-stage renal failure (yes, no)
- Predicted log-odds of acute hospital mortality from the ICNARC\(^{H-2015}\) risk prediction model (linear)
- Sepsis-3 (no sepsis, sepsis, septic shock)
- Vasopressor infusions received at randomisation (none or norepinephrine < 0.1 \( \mu \text{g kg}^{-1} \text{min}^{-1} \), norepinephrine \( \geq 0.1 \mu \text{g kg}^{-1} \text{min}^{-1} \), metaraminol, other/combination)

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.\textsuperscript{15}

5.2.2 Secondary outcomes

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

The number and percentage of deaths at discharge from the critical care unit and acute hospital will be reported within each treatment group. Differences in mortality will be compared, unadjusted, using Fisher’s exact test and, adjusted, using multilevel logistic regression – adjusted for the same baseline variables as the adjusted analysis of the primary outcome.

5.2.2.2 Duration of survival to longest available follow-up

Kaplan Meier curves by treatment group will be plotted up to the longest available follow-up 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.

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

The number and percentage of patients receiving advanced respiratory and renal support, the median (IQR) duration of each support among those that receive it, and the mean (SD) duration of each support among all patients (with those not receiving the support having a duration of 0 days) will be reported within each treatment group. Differences between the groups in the mean duration of support 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 outcome – using bootstrapping to account for anticipated non-normality in the distribution.\textsuperscript{16}

5.2.2.4 Days alive and free of advanced respiratory and renal support

The mean (SD) number of days alive and free of advanced respiratory and renal support to day 28 will be reported within each treatment group. Differences between the 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 outcome – using bootstrapping to account for anticipated non-normality in the distribution.

5.2.2.5 Duration of critical care unit and acute hospital stay

The median (IQR) duration of critical care unit and acute hospital stay will be reported within each treatment group for survivors and non-survivors at discharge from the critical care unit/acute hospital. Differences in durations of stay between the groups will be tested using the Wilcoxon rank-sum test, stratified by survival at discharge from the critical care unit/acute hospital.

5.2.2.6 Cognitive function at 90 days and one year

The mean (SD) IQCODE total score among survivors at 90 days and one year will be reported within each treatment group. Differences between the 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 outcome. This outcome will be reported for patients surviving to the relevant timepoints.

5.2.2.7 Health-related quality of life at 90 days and one year

The mean (SD) EQ-SD-5L health utility among survivors at 90 days and one year will be reported within each treatment group. Differences between the 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 outcome. This outcome will be reported for patients surviving to the relevant timepoint.

5.3 Handling of missing data
As the amount of missing data is anticipated to be minimal, a sensitivity approach will be taken when the primary outcome variable is missing. 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.

Secondary outcomes of cognitive function at 90 days and one year and health-related quality of life at 90 days and one year will be imputed among patients known to be alive at those time points. 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.

5.4 Adherence adjusted analyses
The primary analysis will be repeated adjusting for adherence to allocated intervention (binary variable, as defined in 3.2.2) using a structural mean model with an instrumental variable of allocated treatment to estimate the complier average causal effect of treatment.17

5.5 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.

5.6 Statistical software
All analyses will be conducted in Stata/SE Version 14.2 64-bit x86-64 (StatCorp LLC, College Station, TX).
References
Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension: The 65 Trial

Statistical Analysis Plan, Version 2.1

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Roles and responsibilities

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### Version history

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<td>Descriptive summary statistics added to report fluid balance and urine output, and concomitant medications (inotropes and steroids), by arm</td>
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1. Introduction

1.1 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 the cardiac workload, are mainstays of treatment.

Permissive hypotension refers to the acceptance of blood pressure targets slightly below conventional levels and echoes other permissive therapeutics in the areas of mechanical ventilation (permissive hypoxia, permissive hypercapnia) and permissive hypotension in trauma.¹

There is some evidence that overuse of vasopressors may be harmful, especially in older patients who are more vulnerable to iatrogenic complications in general. A recently completed individual patient data meta-analysis of data from two trials suggests that targeting higher MAP values of between 75 and 85 mmHg, achieved through increased use of intensive interventions, may be associated with an increased risk of death in older critically ill patients.²

In the context of this emerging evidence, doctors and nurses are faced with the challenge of balancing the risks of hypotension against the risks associated with larger doses of vasopressors.

The 65 Trial is testing the hypothesis that the benefits associated with permissive hypotension (and reduced exposure to vasopressors) in older patients will outweigh the risks associated with lower MAP values.

This document describes the proposed statistical analyses for the 65 Trial, and has been prepared in accordance with recent published guidelines³ and includes a fully integrated economic evaluation.

1.2 Aim
The aim of the 65 Trial is to evaluate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) in critically ill patients aged 65 years or over with vasodilatory hypotension.

1.3 Objectives
To estimate the clinical and cost-effectiveness of permissive hypotension (MAP target range 60-65 mmHg whilst receiving vasopressors) when compared with usual care.
2. Study Methods

2.1 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 (MAP target range 60-65 mmHg whilst receiving vasopressors) or usual care.

2.2 Randomisation

Patients are randomised using a dedicated telephone or web-based randomisation service available 24 hours/seven days per week. Allocation is by randomised permuted blocks (with variable block lengths), stratified by recruiting site. As this is a large trial, the risk of chance imbalance in prognostic factors is low and the need to randomise patients during a very short time-frame mandates that the randomisation process is as simple as possible. For these reasons, we elected not to stratify the randomisation process on any baseline covariates.

2.3 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 Case Mix Programme data for patients aged 65 years or older admitted to critical care and receiving advanced cardiovascular support), 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 protocol amendment to the protocol (from version 2.0 to version 3.0), the expected absolute risk reduction was changed from 8% to 6% (expected 90 days 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 vasopressor therapy in the control group was recorded as lower than expected, suggesting that the difference in treatment (and hence outcome) between arms may be smaller than initially anticipated.

2.4 Framework

All outcomes will be tested for superiority.

2.5 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 10 mg (norepinephrine equivalent) in mean total vasopressor dose and/or a separation of 5 mmHg in peak MAP whilst receiving vasopressors
- A minimum of 50 sites open to recruitment
- The recruitment rate in open sites is at least 80% of anticipated

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 of the DMEC to continue or to terminate recruitment.

2.6 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 their one-year follow-up and the final patient recruited has completed their 90 day follow-up. Following the end of the Trial, any patients remaining in follow-up will be censored, the trial database will be locked and the final analysis conducted.

2.7 Timing of outcome assessments
The timings of all outcomes 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).
3. Statistical Principles

3.1 Confidence intervals and P values
All statistical tests 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 subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects.4, 5

3.2 Adherence and protocol deviations

3.2.1 Exposure
Exposure to the intervention will be assessed by the following parameters, calculated for each treatment group:

- Mean arterial pressure – mean (SD) and median (IQR) of the (1) highest and (2) mean MAP for each patient whilst receiving vasopressors, and difference in means with 95% confidence interval
- 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 – mean (SD) and median (IQR) of the total duration (hours) from the later of the 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 comes first), and difference in means with 95% confidence interval
- Dose-rate of vasopressors when given as a continuous infusion – mean (SD) and median (IQR) of the (1) highest and (2) mean rate of norepinephrine equivalents ($\mu g kg^{-1} min^{-1}$) and metaraminol (mg h$^{-1}$), and difference in means with 95% confidence interval
- Total dose of vasopressors (from either infusion or bolus) – the median (IQR) among patients receiving the relevant vasopressor(s) and mean (SD) among all patients (including those not receiving the vasopressor(s) with a value of 0) of the total dose (mg) of vasopressors for (1) norepinephrine, epinephrine, dopamine, phenylephrine and vasopressin combined, expressed as norepinephrine equivalent (see below), (2) metaraminol, and (3) terlipressin, and difference in means with 95% confidence interval
- Total number of episodes of vasopressor treatment (recommencing vasopressors after 24 hours without vasopressor treatment defines the start of a new episode) – mean (SD) and median (IQR) of the number of treatment episodes at critical care discharge, and difference in means with 95% confidence interval
- Total number of days on vasopressors at critical care discharge – mean (SD) and median (IQR) of the total number of days on vasopressors, and difference in means with 95% confidence interval
- Fluid balance – mean (SD) and median (IQR) of fluid balance (ml), measured as the cumulative sum of daily fluid balance during the first episode of vasopressor treatment
- Urine output – mean (SD) and median (IQR) of the mean daily urine output (ml/kg/hr) during the first episode of vasopressor treatment
The distribution across patients of the daily values of the following parameters in each group will be presented in the form of box and whisker plots for days 1-7 following randomisation among all patients receiving vasopressors on that day:

- Mean arterial pressure – (1) highest and (2) mean MAP for each patient whilst receiving vasopressors
- Dose-rate of vasopressor infusion – (1) highest and (2) mean rate of norepinephrine equivalents ($\mu g \ kg^{-1} \ min^{-1}$) and metaraminol (mg h$^{-1}$)
- Daily fluid balance (ml)
- Daily urine output (ml/kg/hr)

The numbers of patients included on each day will be reported at the foot of the figure. Time to discontinuation of vasopressors will be illustrated using Kaplan-Meier curves by group, with time measured in hourly intervals from randomisation (rounded down to the nearest whole hour). Time of discontinuation is defined as the start of the first period of 24 consecutive hours not on vasopressors. Patients who have died, refused deferred consent or withdrawn consent while on vasopressors will be censored on the last recorded dose time.

Norepinephrine equivalents will be calculated using the following two alternate conversion methods$^{18,19}$:

Table 1. Alternate conversion methods for calculating norepinephrine equivalents

<table>
<thead>
<tr>
<th>Vasopressor</th>
<th>Unit</th>
<th>Conversion factor for norepinephrine equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>$\mu g \ kg^{-1} \ min^{-1}$</td>
<td>$\times 1$</td>
</tr>
<tr>
<td>Dopamine</td>
<td>$\mu g \ kg^{-1} \ min^{-1}$</td>
<td>$/150$</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$\mu g \ kg^{-1} \ min^{-1}$</td>
<td>$\times 0.1$</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>U min$^{-1}$</td>
<td>$\times 2.5$</td>
</tr>
<tr>
<td><strong>Method 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>$\mu g \ kg^{-1} \ min^{-1}$</td>
<td>$\times 1$</td>
</tr>
<tr>
<td>Dopamine</td>
<td>$\mu g \ kg^{-1} \ min^{-1}$</td>
<td>$\times 0.01$</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$\mu g \ kg^{-1} \ min^{-1}$</td>
<td>$\times 0.45$</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>U min$^{-1}$</td>
<td>$\times 5 \times 100/\text{weight (kg)}$</td>
</tr>
</tbody>
</table>

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 exploratory graphical approaches will be used to further visually summarise treatment pathways by arm. These will not incorporate any formal statistical comparisons beyond those specified in this SAP.

3.2.2 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 (65 mmHg) 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 the trial data, will trigger a query to the participating site who will 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 may determine that the event did not 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 not having experienced any 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 blood pressure within target range; total time on vasopressors with recorded blood pressure above target range; total time on vasopressors with recorded blood pressure more than 5 mmHg above upper limit of target, and total time on vasopressors with recorded blood pressure below target range. These measures will be summarised as mean, standard deviation, median and IQR.

3.3 Co-interventions

The following parameters will be calculated for each treatment group:

- Receipt of inotropes – the number and percentage of patients receiving inotropes (any of Dobutamine, Milrinone or Levosimendan) at any time during the first recorded episode of vasopressor treatment
- Receipt of corticosteroids – the number and percentage of patients receiving corticosteroids at any time during the first recorded episode of vasopressor treatment

3.4 Analysis populations
All analyses will adhere to the intention to treat principle. The patients will be analysed according to the initial treatment assignment, irrespective of whether the allocated treatment was received. All patients for whom the primary outcome is known will be included in the analysis, regardless of protocol adherence.
4. Trial Population
4.1 Screening data
All participating sites have been asked to keep a Screening Log of all patients accepted for admission to the critical care unit, aged 65 years or older with vasodilatory hypotension and receiving vasopressors – including those who are randomised, and those who are not. The following summaries will be presented:

- Total number of days screening, calculated as the sum of the number of days screening at each site
- Number of screened patients
- Number of eligible patients (% of screened patients)
- Number of recruited patients (% of eligible patients) and reasons for non-recruitment, where known

The recruitment rate per site per month, defined as number of recruited patients/(total number of days screening×12/365), will be calculated both overall (reported with 95% confidence interval, assuming a Poisson distribution) and by site and summarised across sites by the median (IQR).

4.2 Eligibility
The eligibility criteria are as follows.

Inclusion criteria:

- Age 65 years or older
- Vasodilatory hypotension as assessed by treating clinician
- Started infusion* of vasopressors within prior 6 hours (if noradrenaline, then a minimum dose of 0.1 μg kg\(^{-1}\) min\(^{-1}\))
- Adequate fluid resuscitation is completed or ongoing
- Vasopressors expected to continue for 6 hours or more as assessed by treating clinician

*for at least one hour. At the start of the trial patients were eligible if a decision to start vasopressors was made by the treating clinician or the patients had started vasopressors within prior 6 hours, at any dose level. This was amended in v2.0 of the protocol (dated 29th November 2017) to specify that all patients must have started vasopressors within the prior 6 hours, and a minimum dose of noradrenaline was defined.

Exclusion criteria:

- Vasopressors being used solely as therapy for bleeding, acute ventricular failure (left or right) or post-cardiopulmonary bypass vasoplegia
- Ongoing treatment for brain injury or spinal cord injury
- Death perceived as imminent
- Previous enrolment to the 65 Trial

Among those screened (aged 65 years or older and receiving vasopressors), 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 6 hours or more, and (3) meeting each of the exclusion criteria will be reported.
4.3 Recruitment

A CONSORT flow diagram 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
- excluded from the primary analysis (with reasons)

A full description of the consent process is given in the trial protocol, which is summarised in this section. Patients 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; use of their information to support future research. The 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 no longer be an emergency. If the patient does not have capacity following the emergency situation, a personal consultee (relative or close friend of the patient) is asked for their opinion on the patient’s wishes, subsequently patients are approached for consent in person prior to discharge. In the rare event that the patient is discharged prior to consent/opinion being obtained, a telephone/postal mechanism is in place to obtain consent. Where a patient (or consultee) is approached by post and does not reply, they are assumed to have given consent to all components of the trial.

In the event that the patient passes away soon after randomisation prior to them, or their personal consultee, being approached for consent - an independent nominated consultee will be approached to provide consultee opinion.

Patients for whom consent has not been obtained for continued trial participation (e.g. trial treatment) will be included in the analysis of the primary endpoint and all other secondary endpoints (unless otherwise specified).

Patients for whom consent has not been obtained for follow-up questionnaires will have missing data imputed in order to be included in the analysis of cognitive function and health-related quality of life at 90 days and one year (if known to be alive at these time points), and will be included in the analysis of all other endpoints (unless otherwise specified).

Patients for whom consent has not been obtained to access medical records will be included in reporting of baseline characteristics and trial treatment (as this data is gathered directly from source using trial specific CRFs), but will not be included in those endpoints which are analysed using data retrospectively obtained from linked datasets (all mortality endpoints and overall survival, duration and days free from organ support, duration of unit and hospital stay) and will not be included in analysis of patient-reported outcomes (since these outcomes are reported only for patients known to be alive from medical records).
4.4 Withdrawal/follow-up
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

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 analysis, 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 outcomes (as a percentage of survivors) at 90 days and one year will be reported in each group.

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

The total lost to follow-up for 90-day questionnaire follow-up will include both consented patients for whom data is unavailable (true loss to follow-up), and those who withdrew and those for whom consent to receipt questionnaires was never given. The baseline characteristics (as described in Section 4.5) of patients completing a follow-up questionnaire at each time point will be compared with those of patients known to be alive at that time point that did not complete a follow-up questionnaire. The same approach will be taken for one year questionnaires (noting that one year follow-up is curtailed).

4.5 Baseline patient characteristics
The following baseline demographic and clinical data will be summarised for each treatment group but not subjected to statistical testing:
• Demographics
  o Age – mean (SD)
  o Sex (male, female) – number (%)
• Comorbidities – number (%)
  o Chronic hypertension (yes, no)
  o Chronic heart failure (yes, no)
  o 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) – number (%)
• 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) – number (%)
• Acute severity of illness from first 24 hours following admission to the unit
  o APACHE II Score7 – mean (SD)
  o ICNARC Physiology Score8 – mean (SD)
  o ICNARCn=2015 model predicted risk of death9 – median (IQR)
  o Sepsis-310, 11(no sepsis, sepsis, septic shock) – number (%)
• Mean arterial pressure (mmHg) at randomisation – mean (SD)
• Vasopressor infusions received at randomisation – number (%)
  o None*
  o Norepinephrine equivalent < 0.1 μg kg⁻¹ min⁻¹†
  o Norepinephrine equivalent ≥ 0.1 μg kg⁻¹ min⁻¹
  o Metaraminol
  o Other/combination (details in footnote)
• Duration of vasopressor infusion prior to randomisation (minutes) – median (IQR)

*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

5. Clinical Effectiveness Analysis
5.1 Primary clinical outcome
The primary clinical outcome is 90-day mortality, defined as death due to any cause by 90 days
following randomisation.

5.2 Secondary clinical outcomes
5.2.1 Mortality at discharge from the critical care unit and acute hospital
Mortality at discharge from the critical care unit will be 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 leave acute hospital.

5.2.2  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.

5.2.3  Duration of advanced respiratory and renal support during the critical care unit stay
Advanced respiratory support and renal support will be defined according to the UK Department of Health Critical Care Minimum Dataset (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 outside of the critical care unit will be assumed to be free of organ support.

5.2.4  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 and renal support to day 28 will be defined as the number of calendar days (00:00 to 23:59) on which neither advanced respiratory support nor renal support was not received at any time. Patients dying between randomisation and day 28 will be assigned a value of 0.

5.2.5  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 days) from the date and time of randomisation to the date and time of first discharge from the critical care unit or death in the critical care unit, plus the duration of any subsequent admissions to the 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.

5.2.6  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), with the total score calculated as the mean of the scores (from 1 to 5) on the sixteen items.

5.3 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\textsubscript{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\textsuperscript{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.\textsuperscript{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\textsuperscript{-1} min\textsuperscript{-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. 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.

6. 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.

6.1 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.\textsuperscript{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.

6.2 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.

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.
6.3 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\textsuperscript{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).

6.4 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.

6.5 Sensitivity analysis for cost-effectiveness
6.5.1 Sensitivity analyses at 90 days
The following sensitivity analyses will be performed to check the robustness of primary CEA results at 90 days.

\textit{a. 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\textsuperscript{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\textsuperscript{19}.

We will use Bayesian pattern-mixture models, informed by expert elicitation, to allow departures from MAR for missing EQ-5D-5L values\textsuperscript{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 (e.g. Gamma).

\textit{b. Cost data}
Because of the likely skewed distribution of costs we will consider several cost distributions that can give a better fit of cost data (e.g. Gamma).

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

6.5.2 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 at 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 QoL of those patients who are alive and not censored.

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. 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. 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. Quality of life calculated at twelve months will be assumed to apply to each subsequent year of life, after allowing for decrements in quality of life 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.

6.5.3 Analysis across subgroups
The results of the cost-effectiveness analysis will be reported at 90 days across subgroups set out in the clinical analysis (see section 5.2.1).

7. 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 nonmissing 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 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\textsuperscript{28} 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\textsuperscript{29}.

8. 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.

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

22 Lin DY; Linear regression analysis of censored medical costs, Biostatistics, Volume 1, Issue 1, 1 March 2000, Pages 35–47, https://doi.org/10.1093/biostatistics/1.1.35
Statistical analysis plan summary of changes

Statistical analysis plan v1.0, 28 February 2018
Original statistical analysis plan, registered prior to interim analysis

Statistical analysis plan v2.0, 06 March 2019

1) Update to sample size calculation to reflect protocol amendment to version 3.0, 19 March 2018.

2) Addition of cost-effectiveness methods.

3) Addition of subgroup analysis of secondary outcomes by presence of chronic hypertension at baseline.

Statistical analysis plan v2.1, 18 July 2019

1) Descriptive summary statistics added to report fluid balance, urine output, pure intropes administration and corticosteroids by arm.