



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

NHS
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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.

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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 hypoxia¹, permissive hypercapnea²) and permissive hypotension in trauma³.

Current guidelines recommend maintaining mean arterial pressure (MAP – a person's average blood pressure) above 65 mmHg⁴. 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-analysis⁵ 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 trial⁷ 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, SEPSISPAM⁶, 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 $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$)
- 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

- 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 (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 treatment⁸. 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).

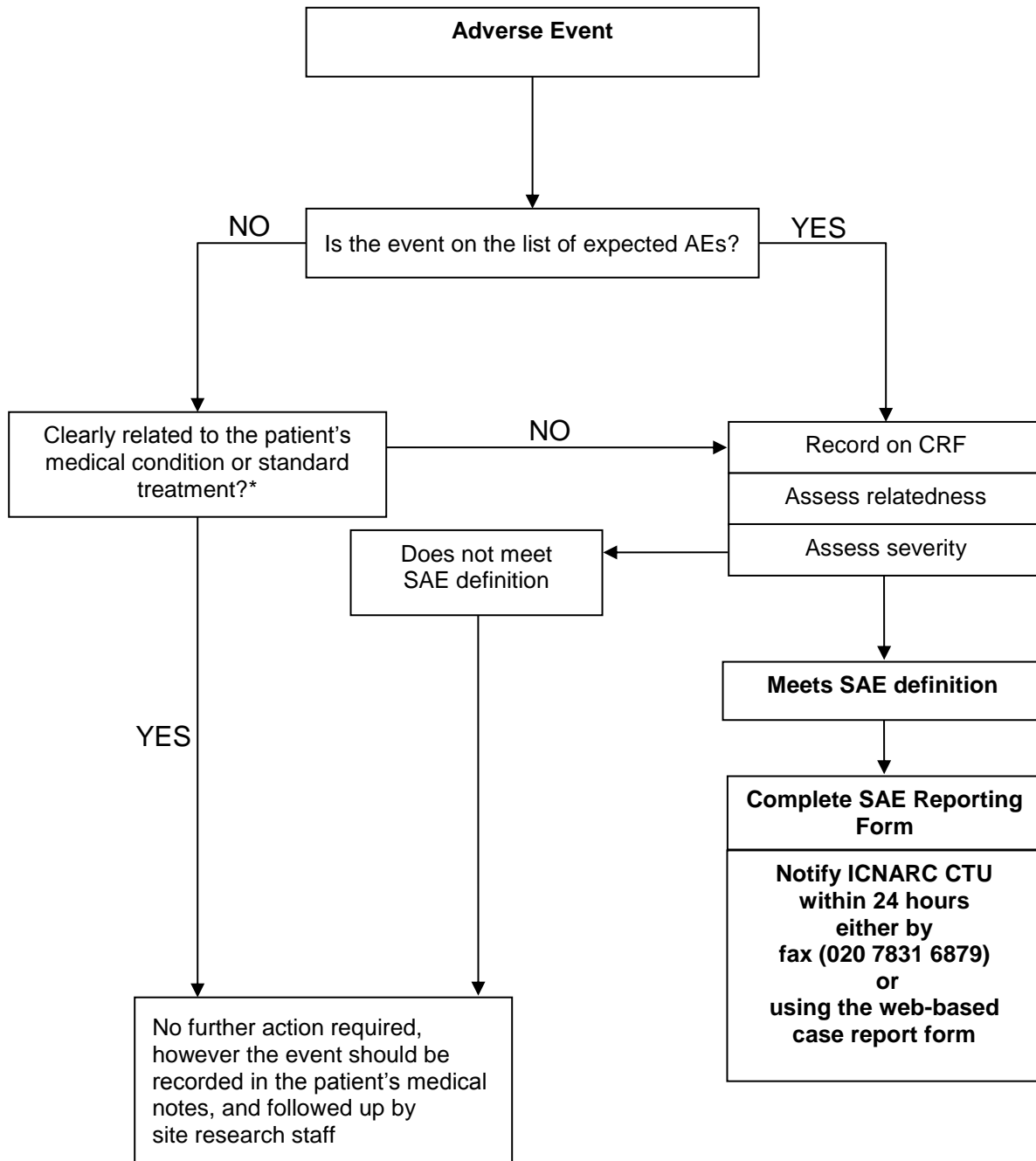
4.8 Additional safety monitoring

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



*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 Procedure⁹, 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

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Appendix 1 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.1	21 April 2017	Alvin Richards-Belle	<ul style="list-style-type: none"> • Section 3.3 (Recruitment and consent) refined • Minor administrative changes
NSA1	1.2	23 May 2017	Alvin Richards-Belle	<ul style="list-style-type: none"> • Section 6.2.1 (Feasibility stage) amended to correct the pre-specified feasibility criteria • Section 3.4.1 (Intervention) clarification added for the situation where a patient develops an exclusion criteria post-randomisation • Minor administrative changes
SA1	2.0	29 November 2017	Alvin Richards-Belle	<ul style="list-style-type: none"> • Section 3.2.1 (Inclusion criteria) refined • Section 4.5 (Recording and reporting procedures) and Appendix 2 corrected • Minor administrative changes
SA2	3.0	19 March 2018	Alvin Richards-Belle	<ul style="list-style-type: none"> • Section 6.1 (Sample size calculation) revised
NSA7	3.1	20 February 2019	Alvin Richards-Belle	<ul style="list-style-type: none"> • Section 4.7 (Questionnaire follow-up) updated • Section 5.1 (End of trial) corrected

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]