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Evaluating the clinical and cost effectiveness of using a permissive blood pressure target to guide titration of vasoactive drugs in critically ill children with hypotension.

STUDY SHORT TITLE

PRESSURE: PRotocolised Evaluation of permiSSive blood pressure targets versus Usual caRE

NHS
National Institute for Health Research

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Chief Investigator
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Steven Kelleher

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 publicly 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:

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Abbreviations

AE	adverse event
ARR	absolute risk reduction
CI	Chief Investigator
CMP	Case Mix Programme
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring & Ethics Committee
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
INB	Incremental net benefit
MAP	mean arterial pressure
NHS	National Health Service
NIHR	National Institute for Health Research
PCCMDS	Paediatric Critical Care Minimum Dataset
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
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

1.1 Background

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

Permissive hypotension refers to the acceptance of blood pressure targets slightly below conventional levels and echoes other permissive therapeutics in intensive care (permissive hypoxia (1, 2), permissive hypercapnia (3, 4)), permissive hypotension in trauma or neonates (5, 6) and permissive temperature targets (7) which have been increasing investigated and recommended in both adult and paediatric intensive care practice.

Current guidelines recommend maintaining mean arterial pressure (MAP – mean arterial or average blood pressure) in the normal range (50th centile for age) (8). However, these guidelines are based on low quality evidence and no guidance is given for an upper MAP limit.

Though interventions to treat hypotension may be lifesaving, there are also harms. Excessive fluids are now known to be associated with prolonged paediatric intensive care unit (PICU) stay and increased mortality (9). Most vasoactive drugs commonly used in children have an alpha-adrenergic effect, causing vasoconstriction, which may reduce blood flow with secondary effects on cardiac, mesenteric, metabolic, microbiome and immune function (10,11). Central venous lines are usually sited to administer vasoactive drugs; these are associated with an increased risk of thrombosis and infection, particularly in very small children in whom the central venous catheter may occupy most of the vessel lumen.

We surveyed 110 members (medical n=62, nursing n= 48) of the UK Paediatric Intensive Care Society in July 2018. 81% of the respondents confirmed their unit set blood pressure targets in over 50% of patients and 79% indicated that in their unit standard practice was for the duty consultant to set the target according to personal preference, in general, somewhere between the 5th and 50th centile (David Inwald, Personal Communication). 92% of respondents stated that they supported the concept of PRESSURE.

1.2 Current evidence

There is some evidence that overuse of interventions, such as vasopressors, to target a high MAP, may be harmful in adults. There have been three trials of a permissive hypotension strategy in critically ill adults. The largest, the 65 Trial (12), showed no harm

from a lower blood pressure target in 2600 critically ill older patients with vasodilatory hypotension.

In a meta-analysis (13) of data from two other adult trials, SEPSISPAM (14) and OVATION (15) suggested that targeting higher MAP values of between 75 and 85 mmHg, may be associated with an increased risk of death in some older critically ill patients.

Each of these trials achieved separation of 10 mmHg difference in MAP values between the treatment groups (higher and lower MAP targets). This led to differences in exposure to vasopressors across the three studies, with the groups targeting lower MAP values receiving significantly lower total doses of vasopressors.

This evidence is solely in adults; therefore doctors and nurses in PICUs are daily faced with the challenging task of balancing the risks of hypotension against the risks associated with vasoactive agents and fluids with no robust trial data to guide them.

PRESSURE is testing the hypothesis that the *benefits* of reduced exposure to medical interventions associated with permissive blood pressure target in critically ill children will outweigh the *risks* of lower blood pressure.

2. Aims and objectives

2.1 Aim

The aim of PRESSURE is to evaluate the clinical and cost-effectiveness of permissive blood pressure targets (lower MAP target 5th centile for age, see Appendix 1 for details) in order to minimise dose and duration of medical interventions in critically ill children with hypotension.

2.2 Objectives

To estimate the clinical and cost-effectiveness of permissive blood pressure targets (lower MAP target 5th centile for age) when compared with usual care.

3. Trial design

PRESSURE 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 17 paediatric intensive care units (PICUs) where PRESSURE will be conducted.

PRESSURE has an anticipated recruitment commencement of the start August 2021 until the end January 2024.

3.1.2 Site requirements

- Compliance with all responsibilities as stated in the PRESSURE 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 paediatric intensive care consultant and one senior paediatric intensive care nurse – both of whom will lead PRESSURE locally
- Identify a PRESSURE Research Nurse responsible for day-to-day local trial coordination
- Agree to incorporate PRESSURE into routine 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
- all relevant institutional approvals (e.g. local confirmation of capacity and capability)
- a fully signed PRESSURE 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 PRESSURE Team at the ICNARC CTU whenever changes are made.

3.2 Population

The target patient population for PRESSURE is critically ill children with hypotension requiring treatment with vasoactive drug(s).

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

3.2.1 Inclusion criteria

- Age >37 weeks corrected gestational age and <16 years
- Accepted for or admitted to PICU
- Receiving a continuous infusion of vasoactive drug for hypotension commenced within previous 6 hours
- Vasoactive drug expected to continue for at least 6 hours or more
- On invasive mechanical ventilation

3.2.2 Exclusion criteria

- Admitted post cardiac surgery
- Known cardiomyopathy
- Neonates with suspected or proven duct dependent circulation
- Brain injury
- Pulmonary hypertension
- Malignant hypertension
- Death perceived as imminent
- Previously recruited to PRESSURE

3.2.3 Co-enrolment

The PRESSURE investigators will consider co-enrolment of PRESSURE participants onto other interventional studies where there is no possible conflict with PRESSURE 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 PRESSURE Case Report Form (CRF).

3.2.4 Screening

Potentially eligible patients admitted (or accepted for admission) to the participating PICU 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. All patients on vasoactive drugs should be recorded in the screening log.

3.3 Recruitment and consent

3.3.1 Randomisation

Eligible patients will be randomised on a 1:1 basis to either permissive blood pressure targets or usual care using a central web-based randomisation service. Randomisation will be stratified by site and age. The randomisation sequence will be computer generated and use variable block sizes to strengthen allocation concealment. The health technologies used in this study cannot be blinded. The randomisation module will issue a target blood pressure for patients allocated to the intervention group.

The trained staff member who randomises the patient will immediately inform the clinical team responsible for the patients care who will commence the randomised treatment as soon as practically possible. In addition, the local site research team will be notified of the randomisation by email. Following enrolment into PRESSURE, each participant will be assigned a unique PRESSURE Trial Number and a CRF will be completed by the local research team.

During the recruitment period a member of the PRESSURE study team will be available 24 hours/seven days per week to address emergency recruitment, randomisation or clinical issues that arise.

3.3.2 Consent procedures

Consent will be sought for the child (patient) from a parent/legal guardian with parental responsibility.

Children who are eligible for PRESSURE become so during a period of critical illness. This is a profoundly stressful time for children's' parents/legal guardians during which time there are ethical concerns both about the burden of trying to understand the trial and the ability of the parent/legal guardian to provide informed consent during a time of great distress. Furthermore, initiation of vasoactive drugs is most often during an emergency time-sensitive situation where any delay to commencing treatment could be detrimental to the patient and to the scientific validity of the trial.

Considering these issues, PRESSURE utilises a deferred consent model ('research without prior consent'). Once a patient is screened and confirmed as eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment will be commenced as soon as possible.

This model, developed in line with the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance (16) has been found to be acceptable to parents/guardians, as well as to clinicians, in several recent RCTs conducted in the paediatric critical care setting (17-20). Findings from these studies have been incorporated into our consent procedures and will be used for training at sites.

3.3.3 Consent prior to hospital discharge - Deferred consent

Once notified of the randomisation of a patient into the study, a trained, delegated member of the site research team will approach the parents/legal guardians of the patient as soon as appropriate and practically possible after randomisation to discuss the study (this will usually occur within 24-48 hours of randomisation). If the participant has died or been discharged from hospital prior to their parents/legal guardians being approached, then the parents/legal guardians will be approached at a later point (see *Discharge prior to consent being sought* and *Death prior to consent being sought*).

Before approaching the parent/legal guardian, the research team member will check with the relevant clinical staff that the participant is stable and that timing is appropriate. If the participant's condition has not stabilised additional time should be allowed before approaching the parent/legal representative. Checks conducted to assess appropriate timing for approach will be recorded in the patients' clinical notes.

Once approached, a Participant Information Sheet (PIS) for parents/legal guardians will be provided. The PIS will identify the title of the study and the Chief Investigator (CI) and include information about: the purpose of the study; the consequences of participating or not; participant confidentiality; use of personal data; data security; and the future availability of the results of the study. 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 to continue data collection, to receive a follow-up questionnaire and for anonymised data to be shared with other researchers in the future. Parents/legal guardians will be given time to read the PIS and have an opportunity to ask any questions they may have about their child's participation in PRESSURE and to discuss with other family members or friends before confirming their decision.

After the person seeking consent has checked that the PIS and Consent Form have been understood, they will invite the parent/legal guardians to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/legal guardians to keep, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to age and severity of illness and its impact on the mental state of the target population, it will not be possible to involve study participants in the consenting process. Instead, assent will be obtained prior to hospital discharge if their condition allows (e.g. they regain mental capacity). Study participants will then be provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate, to confirm they have been informed and understand the study. Parents/legal guardians will be involved in this discussion. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal guardians to discuss with the participant following recovery.

3.3.4 Discharge prior to consent being sought

In the rare situation where the patient is discharged from hospital prior to the parent/legal guardians confirming their consent decision, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal guardians within five working days of hospital discharge to inform them of their involvement in the study and to provide information about the study. Following on from the call, as well as if there is no response to the call, the parents/legal guardians will be sent a covering letter, personalised by the most appropriate member of the site research team or clinical staff member, and a copy of the PIS and Consent Form by post. The letter will direct the parents/legal guardians to the PIS for detailed information on the

study and provide telephone contact details if the parents/legal guardians wish to discuss the trial with a member of the site research team. The letter will ask the parents/legal guardians to return the Consent Form to confirm whether they would like their child to continue participation in the study (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, will be sent to the parent/legal guardians. 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 second letter being sent, then the participant will be included in the study unless they notify the site research team otherwise. In this event, the site research team should document the non-response on a File Note in the Investigator Site File.

If the participant is transferred to another hospital participating in PRESSURE 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.

3.3.5 Death prior to consent being sought

In the rare situation where a participant dies before consent has been obtained, a site research team member will obtain information from colleagues and bereavement counsellors to establish the most appropriate research/clinical team member to notify the parents/legal guardians of the involvement in the study. Deferred consent can be sought from parents/legal guardians following the death of their child and prior to their departure from the hospital; however, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Participant Information Sheet for bereaved parents/legal guardians (B-PIS) and Consent Form (bereaved) would be used.

If deferred consent is not sought prior to the parents'/legal guardians' departure from the hospital, then the parents/legal guardians will be sent a covering letter, personalised by the most appropriate research/clinical team member, and a copy of the B-PIS and Consent Form (bereaved) by post four weeks after randomisation. Where possible, the clinical or research team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the B-PIS for detailed information on the study and provide telephone contact details if parents/legal guardians wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the B-PIS and Consent Form for bereaved parents/legal guardians will be sent to the bereaved family. This second letter will provide the same information as the first letter. In addition, this letter will also 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 study.

3.3.6 Refusal or withdrawals of consent

If informed consent is refused or withdrawn, this decision will be respected and abided by, and no further contact made. All data occurring up to the point of this decision will be retained and a minimised anonymised dataset will be collected and retained for monitoring safety and important outcomes in the trial, unless the parent/legal guardian requests otherwise.

3.4 Procedures

3.4.1 Intervention

Patients in the intervention group will be treated using permissive blood pressure target (lower MAP target 5th centile for age (21) – see Appendix 1 for details) whilst receiving vasoactive drugs in order to minimise dose and duration of medical intervention.

The decision to discontinue vasoactive drugs will depend on the patients' ability to maintain the permissive blood pressure target stipulated by the protocol without vasoactive drugs. Clinical teams will be actively reminded to consider discontinuing vasoactive drugs if the patients are able to maintain MAP values of at least the 5th centile for age. The trial treatment will apply at any point the patient requires vasoactive drugs whilst on PICU during the acute hospital admission. In the intervention group, vasoactives should only be restarted if MAP is lower than 5th centile for age (i.e. below the lower end of the treatment range specified in Appendix 1).

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 permissive blood pressure 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 vasoactive drugs (noradrenaline/norepinephrine, adrenaline/epinephrine, dopamine, dobutamine, metaraminol, milrinone, phenylephrine, vasopressin, terlipressin), use of fluid bolus therapy and corticosteroids will be recorded but left to the discretion of the treating team.

As per usual clinical care of patients receiving vasoactive drugs, central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) will often be in place.

3.5 Outcomes

Primary outcome - Clinical effectiveness:

- composite of mortality and duration of ventilator support, defined by the Paediatric Critical Care Minimum Dataset (PCCMDS), from randomisation to day 30

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 PICU discharge, 30 days, 90 days and 12 months
- duration of survival to 12 months
- time to liberation from invasive ventilation
- functional status change between PICU admission and PICU discharge, measured by the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales (22)
- receipt of renal replacement therapy at 30 days
- length of PICU and hospital stay
- Health-related quality of life (HrQoL) at 1 year, measured by the child self-or parent-proxy reported PedsQL-4.0 (23) with age-appropriate versions covering the wide range included in the trial (1 month-16 years) and the Child Health Utility 9D Index (CHU-9D) (24)
- Incremental costs at 30 days

3.6 Data collection

To maximise the efficiency of the design, data collection for PRESSURE will be linked to the routine data collection for the PICANet audit. Data from PICANet used in the trial analysis will include:

- baseline demographics.
- risk factors included the paediatric index of mortality score.
- critical care daily interventions, based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.

All patients recruited to the trial will be informed regarding data linkage with other routine data sources. Data obtained from routine data sources will include:

- date of death for deaths occurring after discharge from acute hospital, by data linkage with death registrations (NHS Digital); and
- hospital costs for subsequent hospitalisations, by data linkage with Hospital Episode Statistics (NHS Digital).

Additional data items collected specifically for the trial will be limited to the minimum required to deliver the trial objectives. These will include:

- name, address and telephone number for questionnaire follow-up
- data items to confirm eligibility
- baseline data to characterise patients, including severity of illness scoring and comorbidities
- data to monitor adherence with the treatment protocol and separation between treatment groups, including MAP values, vasoactive drug doses/durations and fluid boluses administered
- functional status (PCPC and POPC) prior to PICU admission and at PICU discharge
- calendar days of organ support received during PICU
- time to extubation
- location of care
- hospital transfers / discharge
- co-enrolment with other studies
- adverse event reporting

Data will be recorded in trial case report forms at participating sites and will be entered at site onto an electronic case report form (secure data entry system setup at ICNARC CTU), where they will undergo checks for accuracy, completeness and consistency.

If the patient has died prior to the parent/guardian being approached for consent, identifiable data for questionnaire follow-up and data regarding functional status will not be recorded. In this situation, if the parent/guardian refuses consent, a minimised data set will be retained to monitor safety and important outcomes.

3.7 Questionnaire follow-up

Each participant will be followed up with a questionnaire at 12 months post-randomisation to assess HrQoL. Prior to the sending of a questionnaire, survival status will be ascertained either through review of medical records by local research teams and/or via data-linkage with nationally held records (decedents will be logged in the trial records and the follow-up process ended).

At the 12-month time point, parents/legal guardians of recruited patients will be emailed or posted (as per their preference indicated at the time of consent) a questionnaire by the ICNARC CTU containing the PEDS-QL and CHU-9D). The questionnaires are designed to take no longer than 15 minutes to complete. If a parent requests a questionnaire to be sent via post, then a pen and self-addressed stamped envelope will be provided for ease of return.

If there is no response within three weeks, parents/legal guardians will be telephoned and asked to confirm whether they have received the questionnaire. If needed, they will be offered the option of either being sent another copy of the questionnaire (via email or post), or to complete the questionnaire over the telephone with a trained member of the PRESSURE trial team.

If a patient is an in-patient at a participating site at the follow-up time-point, the site research team will be asked to approach the parent/legal guardian and, if willing, conduct the questionnaire with the parents/legal guardians in 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

Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs).

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 (AE) is defined as any untoward medical occurrence or effect in a patient participating in a study. It does not necessarily have to have a causal relationship with the study treatment.

Serious Adverse Event

A Serious Adverse Event (SAE) is defined as an Adverse Event that:

- 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.

"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.

"Hospitalisation", refers to inpatient admission, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.

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.

Unexpected and Related Serious Adverse Event

A suspected Adverse Event related (possibly, probably or definitely) 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

The PI, or other medically qualified investigator as listed on the Delegation Log, should assess severity, relatedness and expectedness, categorised as follows:

- **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 causal relationship to the study treatment
- **Unlikely**: there is little evidence to suggest a causal relationship to the study treatment (e.g. because the event did not occur within a reasonable timeframe after administration of the trial treatment), and there is another reasonable

explanation of the event (e.g. the participant's clinical condition, other concomitant medications).

- **Possibly**: there is some evidence to suggest a relationship to the study treatment (e.g. because the event occurred within a reasonable timeframe after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).
- **Probably**: there is probable evidence to suggest a causal relationship to the study treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a causal 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

Occurrences of the specified, expected adverse events (Appendix 2) will be recorded for all randomised patients from the time of randomisation until critical care unit discharge

Considering that all children eligible for PRESSURE are critically ill and, due to the complexity of their condition, are at an increased risk of experiencing AEs – occurrences of non-specified, unexpected adverse events will only be reported if they are considered to be possibly, probably or definitely causally related to the study treatment, specifically due to administration of vasoactive drugs or the patient's blood pressure.

The following events are exempt from reporting as AEs or SAEs

- Deterioration of condition or death that is not related to the trial intervention.
- Reaction to non-trial medication.

All Adverse Events that occur between randomisation and critical care unit discharge must be recorded in the patients' medical notes, as well as on the PRESSURE safety monitoring CRF and PRESSURE SAE Reporting Form where appropriate. PRESSURE SAE Reporting forms should be uploaded to the web-based data entry system within 24 hours of becoming aware of the event. Sites should also email pressure@icnarc.org to inform the trial team the event has been uploaded on the SAE reporting form.

Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available. However, essential criteria regarding date and

time onset, event name, severity and relatedness of the event to the study treatment must be recorded in the first instance.

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 an SAE report, a member of the ICNARC CTU will first evaluate the report for completeness and internal consistency. Then, a clinical member of the PRESSURE Trial Management Group (TMG) will evaluate the site's assessment of the event for severity, relatedness and expectedness to determine whether the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

4.8 Additional safety monitoring

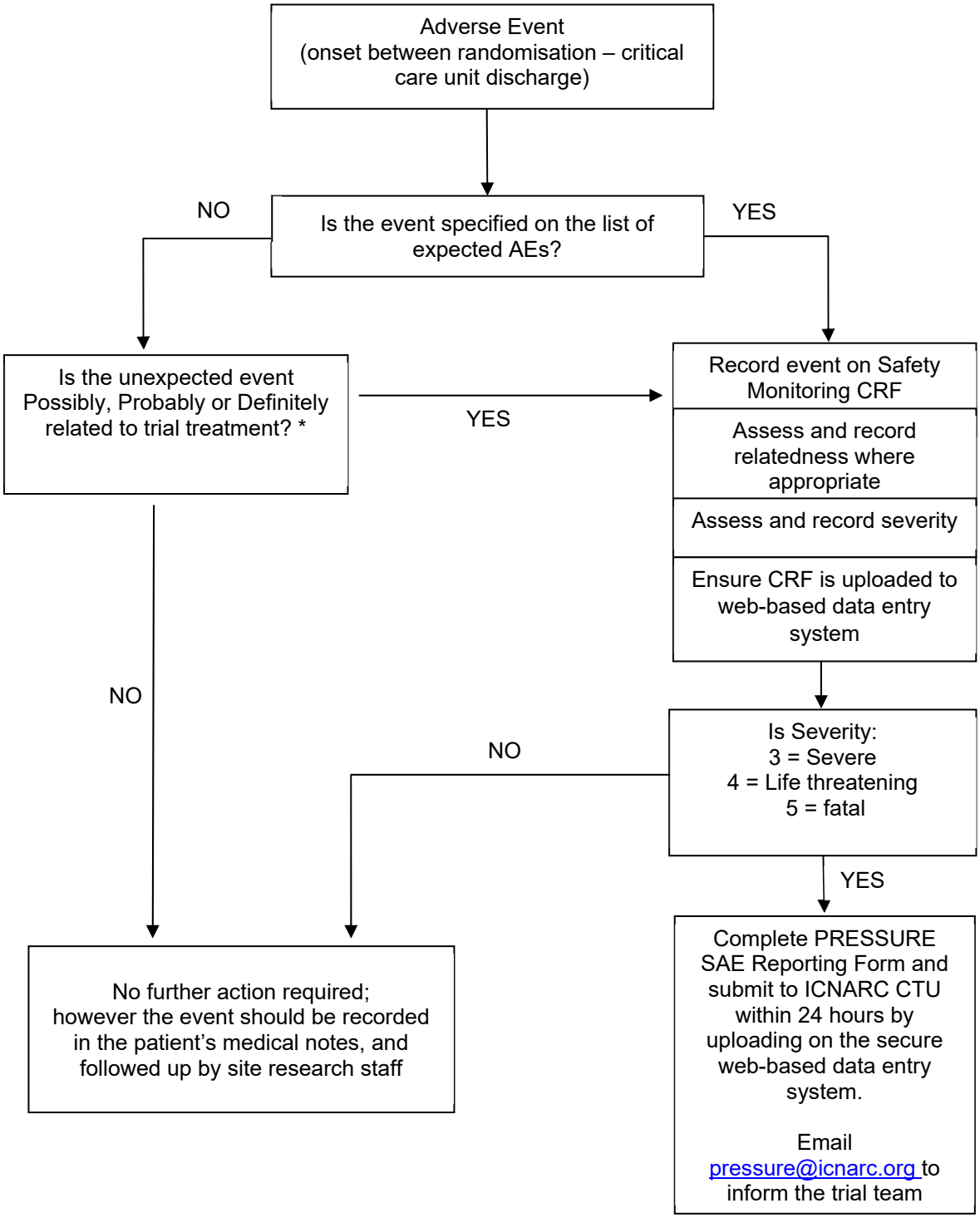
The ICNARC CTU will also monitor data for any trial related events that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in adverse events, the Trial Management Group will be contacted for their opinion. If it is declared necessary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

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).

4.9 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 trial treatment, then it should be reported.

5. Trial closure

5.1 End of trial

The end of the trial will be when the last patient has completed their 1 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 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 50% of the target sample size 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

In order to power the trial, we estimated the mortality at 30 days, and days on ventilation for patients on usual care, using observational data from the FEVER study (19). This study included three quarters of all the UK PICU/HDU NHS units currently participating in PICANet (22/28) and collected data on 6 months of all eligible sequential admissions

to these units (n=4126, representing 39% of all unplanned admissions to UK NHS units reporting to PICANet in 2017 (25). As our control arm specifies usual care only, this observational data should provide a reliable estimate of the expected distribution of the primary outcome in the control arm. This approach is in line with other paediatric intensive care trials in the UK which have also based their sample size calculations on observational data from PICANet (SANDWICH, CHiP).

Power estimates were based on 10,000 simulated trial datasets, using distributions of mortality (13%) and duration of ventilator support (log-normal distribution with mean 7.8 and standard deviation of 9.5 days). To achieve 90% power to detect a clinically meaningful reduction in mortality of 2% from 13% to 11% and the mean duration of ventilator support of 18 hours from 7.8 to 7.1 days, and allowing for 10% withdrawal/refusal of deferred consent, we will recruit a total sample size of 1900 patients. The same sample size will retain at least 80% power with either a mean reduction of 15 hours ventilator support and a 2% reduction in mortality, or a mean reduction of 18 hours ventilator support and a 1% reduction in mortality. Code and output from the sample size simulations are available on request.

6.2 Statistical analysis

6.2.1 Internal pilot stage

PRESSURE will use a traffic light system (26) to assess progression from the internal pilot phase (first six months of the recruitment period) to full trial using the following criteria:

Green light (go)

1. A minimum of 10 sites are open to recruitment
2. The overall recruitment rate in open sites is at least 75% of anticipated
3. Separation in the mean MAP of at least 5 mmHg whilst receiving vasoactive drugs between the groups
4. Separation in the mean duration of vasoactive drug of at least 12 hours between the groups.

Amber light (amend)

1. 6-9 sites are open to recruitment
2. The overall recruitment rate in open sites is 40-75% of anticipated
3. Separation in the mean MAP of 2.5-5 mmHg whilst receiving vasoactive drugs between the groups
4. Separation in the mean duration of vasoactive drug of 3-12 hours between the groups

Red light (stop)

1. Fewer than 6 sites are open to recruitment
2. The overall recruitment rate in open sites is less than 40% of anticipated
3. Separation in the mean MAP of less than 2.5 mmHg whilst receiving vasoactive drugs between the groups
4. Separation in the mean duration of vasoactive drug of less than 3 hours between the groups

If all the green criteria are met, the study will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, the study will be amended to address the issues raised. If any of the red criteria are met, the study will stop.

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 follow the intention to treat principle. Baseline patient characteristics will be compared between the two groups to observe balance and the success of randomisation. These comparisons will not be subjected to statistical testing. The delivery of the intervention will be described in detail.

The analysis of the primary, composite, outcome will use rank-based methods, with death during the first 30 days following randomisation ranked as the worst outcome and surviving patients ranked according to their duration of ventilator support (27). The ranked outcomes will be compared between groups using a two-sample rank-sum (Wilcoxon-Mann-Whitney) test. The primary effect estimate will be the probabilistic index (the probability that the intervention is superior to the control for either mortality and/or duration of ventilator support), which will be presented with a 95% confidence interval. The separate components of the composite outcome (duration of ventilation support in surviving patients, and mortality at 30 days) will also be presented by arm with effect sizes and 95% confidence intervals, in line with published guidelines for use of composite primary endpoints (28).

Secondary analyses of mortality will be performed by Fisher's exact test and adjusted logistic regression. Duration of survival to 12 months will be plotted as Kaplan-Meier survival curves, compared unadjusted with the log rank test and adjusted using Cox regression models. Time to liberation from invasive ventilation will be analysed by the log rank test, with patients that die while ventilated treated as censored. Analyses of length of PICU and hospital stay will be performed by rank-sum tests, stratified by survival status. Analyses of functional status and HrQoL will be performed by t-tests and adjusted linear regression. Baseline factors for inclusion in adjusted analyses will be selected a priori based on an established relationship with outcome for critically ill children, and not because of observed imbalance, significance in univariable analyses or by a stepwise selection method.

The primary endpoint, and some important secondary endpoints, will be reported in a limited number of clinically relevant subgroups, which will include patients classified by age. All subgroups will be specified in advance in the analysis plan and results will be interpreted taking into account accepted criteria for credible subgroup effects (42,43).

A single interim analysis will be undertaken following recruitment and follow-up to 30 days of 50% of patients using a Peto-Haybittle stopping rule ($p<0.001$) for termination due to either benefit or harm.

6.2.3 Health economic evaluation

The cost effectiveness analysis (CEA) will take a health and personal health services perspective. Patient-level resource use data from the PICU stay will be taken both from the case report form and linked to routine data from PICANet. PICANet will provide routine data on the level of care for PICU bed-days through collection of the PCCMDS; this can be cross referenced to the CRF if necessary. Information will also be collected on the additional resources (e.g. staff time, medications etc.) required to administer the interventions. Information on subsequent PICU and hospital admissions will be obtained via data linkage with PICANet and Hospital Episode Statistics. Patient-level resource use data will be combined with appropriate unit costs from the NHS payment by results database and Personal Social Services Research Unit to report total costs per patient for up to 12 months since randomisation. Use of primary care and community health services will be assessed by questionnaires at 12 months. Data from the PedsQL and CHU-9D questionnaires at 12 months will be combined with survival data to report QALYs.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 12 months. The CEA will use multilevel linear regression models that allow for clustering of patients at site. The analysis will adjust for key baseline covariates at both patient and site level.

The CEA will also perform a cost-consequence analysis and report incremental costs alongside primary outcome at 30 days.

7. Trial management and oversight

The Chief Investigator (Dr David Inwald) alongside the ICNARC CTU will take overall responsibility for delivery of PRESSURE and oversee progress against timelines/milestones.

7.1 Good research practice

PRESSURE will be sponsored by Cambridge University Hospitals NHS Foundation Trust 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 PRESSURE Investigators (listed on page 5) – led by the Chief Investigator (Dr David Inwald). The day-to-day trial team will comprise the Chief Investigator, CTU co-investigators (Paul Mouncey, Prof David Harrison and Karen Thomas) alongside the Trial Manager (Alanna Brown), Trial Statistician (Karen Thomas), Research Assistant (Robert Darnell) and Data Manager (Stefan Sprinkmoller). 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 Chief Investigator 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

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

8.1 Trial registration

This trial has been registered with the ISRCTN Registry (ISRCTN20609635~~XXXXXXX~~).

8.2 Central ethical compliance

The trial has received a favourable ethical opinion from the Cambridge South Research Ethics Committee (Reference: 21/EE/0084)~~[INSERT Research Ethics Committee (Reference: XXXXXX)]~~ and approval from the Health Research Authority. The ICNARC CTU will submit annual progress reports and all amendments to the PRESSURE 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 PRESSURE, 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 is one PPI representatives as co-investigators on the PRESSURE Trial and who has been involved in its development. As a member 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

Sponsor name:	Cambridge University Hospitals NHS Foundation Trust
Address:	Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ
Contact:	Stephen Kelleher
Email:	research@addenbrookes.nhs.uk

The NHS Clinical Negligence Scheme for Trusts provides full financial liability for harm caused to participants in the study caused through negligence. Cambridge University Hospitals NHS Foundation Trust provides insurance cover for negligent harm caused as a result of the design and management of the study. NHS indemnity does not offer cover for non-negligent harm.

9.2 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: NIHR128895).

10. Dissemination

The results of PRESSURE will be disseminated actively and extensively. This will cover both progress during the trial period and the results at the end of the study. The outputs for PRESSURE will include, but not limited to, the following areas:

- meeting and conference presentations (international and national) of study progress and results;
- publication of study results (1) primary results and (2) longer-term outcomes, including economic evaluation; and
- incorporation into clinical guidelines.

These separate outputs will be targeted at relevant stakeholders in formats suitable for the target audience. This will ensure that the potential benefit of PRESSURE is maximised.

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.

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Appendices

Appendix 1 – PRESSURE Permissive MAP Targets

The PRESSURE clinical reference group, which included five paediatric intensivists and an academic paediatric intensive care nurse, chose to base the lower end of the target on the Haque and Zaritsky data (21) because (a) it is based on data derived from measurements in healthy children outside hospital, and therefore unlikely to be confounded by disease or hospital treatment; (b) it is the data upon which the Paediatric Sepsis Consensus Conference based their definition of systolic hypotension; (c) and the MAP centile tables are cited in in numerous research studies and in use clinically around the world.

For children under 1 year of age, in whom 5th centile data was not reported by Haque and Zaritsky, the range was based on the 5th centile MAP (NIBP) from three London PICUs, observed in our pilot work, with preterm infants excluded (29).

Recent data has shown that outcome post cardiac arrest is worse with systolic blood pressure below 5th centile (30), and current consensus guidelines suggest that in this group of patients, systolic blood pressure below the 5th centile should be avoided (31, 32). Hence the clinical reference group decided that the PRESSURE permissive MAP target should be presented as a range, from at or very near the 5th centile ("lower permissive") to (5th centile + 5mmHg) ("upper permissive"). For older adolescents, the upper permissive MAP target was set at 65 based on recent adult studies (12-15). The lower target was set at 35mmHg for infants up to 1 year of age because of concerns about cerebral (33) or coronary (34) hypoperfusion at a lower MAP.

The clinical reference group also decided that the 5th centile should be given by age banding only. Initial plans to stratify the target band based on gender and height were abandoned because there is relatively little difference in MAP between genders; and height is often not measured, or measured inaccurately, in a PICU setting. For these reasons the PRESSURE permissive MAP target is presented based on an average of male and female 5th centile MAP, for 50th centile height, by age band (Table 1). Where possible, the upper and lower permissive MAP targets were rounded to the nearest multiple of 5mmHg to produce a target band easily understood by bedside staff.

Table 1

PRESSURE permissive MAP target

Age range (completed months/years)	Lower target	Upper target
0 – 5 months	35	40
6 – 11 months	38	43
1 – 2 years	40	45
3 – 5 years	45	50
6 – 9 years	50	55
10 – 13 years	55	60
14 – 16 years	60	65

Appendix 2 - Expected adverse events

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

- Myocardial ischaemia
- Arrhythmia
- Digital or limb ischaemia
- Central line related blood stream infection (CLABSI)
    - *defined as "recovery of a pathogen from a blood culture (a single blood culture for organisms not commonly present on the skin and two or more blood cultures for organisms commonly present on the skin) in a patient who had a central line at the time of infection or within the 48-h period before development of infection".*
- Thrombus related to central line insertion
    - *if of sufficient severity to require systemic anticoagulation*

[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]

Appendix 3– Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	25 February 2021	Alanna Brown	N/A
N/A (changes made before initial approved version of protocol)	2.0	28 April 2021	Alanna Brown	Appendix 1 MAP target altered. References updated
NSA1	2.1	19 May 2021	Alanna Brown	Funder email address updated