Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
PRESSURE

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No

b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No

c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [x] Scotland
- [x] Wales
- [x] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR Medtech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN. ***Submission of a Portfolio Application Form (PAF) is no longer required.***

6. Do you plan to include any participants who are children?

◉ Yes ○ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
PRESSURE

Please complete these details after you have booked the REC application for review.

REC Name:
East of England - Cambridge South Research Ethics Committee

REC Reference Number:
21/EE/0084

Submission date:
08/03/2021

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Dr	David	Inwald
Post	Consultant in Paediatric Intensive Care		
Qualifications	MBBChir FRCPCH FFICM PhD		
ORCID ID	0000 0001 9518 7821		
Employer	Cambridge University Hospitals NHS Trust		
Work Address	PICU Addenbrooke's Hospital Cambridge		
Post Code	CB2 0QQ		
Work E-mail	di260@cam.ac.uk		
* Personal E-mail			

Work Telephone	07917373689
* Personal Telephone/Mobile	
Fax	

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Miss	Alanna	Brown
Address	ICNARC		
	24 High Holborn		
	London		
Post Code	WC1V 6AZ		
E-mail	pressure@icnarc.org		
Telephone	020 7831 6878		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	ICNARC/01/09/20
Sponsor's/protocol number:	A095842
Protocol Version:	1.0
Protocol Date:	25/02/2021
Funder's reference number (enter the reference number or state not applicable):	NIHR128895
Project website:	

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

◯ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

When children are in intensive care, their blood pressure can fall. A low blood pressure (hypotension) can be dangerous, even life threatening. It can cause damage to the brain and other organs. Many intensive care treatments are used to increase blood pressure. These include intravenous fluids and drugs to make the heart pump harder. However, these treatments also have side-effects and complications. Currently, most doctors aim to achieve a blood pressure in the normal range for age. However, recent research in adults shows that it may be safer not to push blood pressure all the way back up to normal, but simply to avoid very low pressures. Unfortunately, in children, there is no clear evidence on which to base practice.

The Paediatric Intensive Care Society and the Intensive Care National Audit & Research Centre (ICNARC), have developed the PRotocolised Evaluation of permiSSive hypotension versus Usual caRE (PRESSURE) study, which aims to find out the best blood pressure target to use for children in paediatric intensive care units (PICUs). We plan to conduct a clinical trial testing a lower blood pressure target (depending upon age) in children with hypotension against current usual practice. In common with other recent emergency trials in children, we will use a 'deferred consent' approach where permission to continue with the study is sought from parents as soon as possible after the emergency care has been provided. To find out which treatment is best, we will compare the amount of time children need support for their breathing and survival in intensive care between the two groups. We will also look at survival and child development after leaving PICU, as well as the total costs of the treatments.

PRESSURE will help us determine the best blood pressure target to use for children with low blood pressure in PICU.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Purpose and design

Hypotension, defined as a systolic or mean blood pressure < 5th centile, is a key feature of shock, which is a common finding in critically ill children. Shock may be caused by infection and numerous other causes. Untreated, hypotension compromises tissue perfusion and organ function, with an increased risk of multiple organ failure and death. Hypotension is also associated with poor neurological outcome in survivors, particularly after cardiac arrest and head injury.

Hypotension is typically treated by administration of fluid boluses and infusions of vasoactive drugs. Around 20,000 children are admitted to intensive care as an emergency in the UK each year, 80% of whom will receive fluid bolus therapy, with at least 30% receiving vasoactive drugs.

Though interventions to treat hypotension may be lifesaving, there are also harms. Excessive fluids are associated with prolonged PICU stay and increased mortality. Most vasoactive drugs have an alpha-adrenergic effect, including dopamine, adrenaline and noradrenaline; these are commonly used in children. These drugs induce vasoconstriction, which may reduce blood flow and cause other secondary effects on cardiac, mesenteric, metabolic, microbiome and immune function. Central venous lines are usually sited to administer these drugs; these are associated with an increased risk of thrombosis and infection, particularly in very small children.

Clinicians in paediatric intensive care are faced with the daily task of trying to balance the risks of hypotension with the risks of harm from fluids, vasoactives and central venous lines. However currently, there is no high-quality evidence from randomised controlled trials (RCTs), comparing blood pressure targets in critically ill children, to guide them in this task.

Therefore, there is an urgent need for high quality evidence to inform the choice of blood pressure targets in critically ill children.

A more permissive blood pressure is an important target to investigate in critically ill children because:

1) Fluid bolus therapy is administered to 80% of paediatric intensive care unit (PICU) patients and vasoactive drugs to 30%.
2) Current practice is generally to target a mean arterial pressure of 50th centile for age.
3) Fluid overload is demonstrably harmful to critically ill children.
4) It is biologically plausible that vasoactive drugs may be directly harmful to critically ill children.
5) Current guidance on blood pressure targets is not based on evidence.

Our observational data from three London PICUs demonstrates that observed MAP is in fact far in excess of the 50th centile for age, despite clinicians' mean stated target (from our 2018 survey) being between the 5th and 50th centile.

Recruitment and Consent

This trial is designed to investigate critically ill children requiring mechanical ventilation and vasoactive drugs for clinician diagnosed hypotension.

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

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

Consent

The main ethical issue arises from the fact the treatment is being given within the context of a medical emergency, where any delay in commencing treatment would be detrimental to the child’s care. This also presents a profoundly stressful situation for parents/guardians during which time there are ethical concerns about both the burden of trying to understand the trial, and their ability to provide informed consent during a time of great distress.

To ensure there is no delay to treatment, it is essential that patients are randomised as soon as they become eligible. Both ranges used within the trial are within recommended ranges and used in current clinical practice – only determined by individual clinician preferences.

We will, therefore, use a deferred consent model (‘research without prior consent’) in PRESSURE. This model was acceptable to parents and clinicians within other previous RCTs conducted in the paediatric critical care setting. This consent model was been informed and refined through extensive PPI work and is based on the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance.

Parents will be fully informed of all data processing for the trial, with identifiable data only processed where consent is in place.

Risks, burdens and benefits

With regards to the clinical treatments, there are no additional risks over and above the known variation in current clinical practice.

As the study will use identifiable and health data, there is a small risk that data could be lost or breached. Robust

measures will be in place to prevent this from occurring – e.g. through the implementation of regular data back-up arrangements and data disaster recovery procedures. To minimise the possibility of data security breaches, all data leaving the recruiting NHS hospital will be sent securely. Identifiable data will only be collected where essential and after informed consent is in place. Participants will be allocated a unique trial number to minimise the processing of identifiable data. Data sharing agreements will be put in place where needed (e.g. between ICNARC and NHS Digital to permit data linkage).

Confidentiality

Patient identifiable data will be required at ICNARC CTU to enable one-year follow-up and to conduct data linkage with national organisations. Only individuals vital to the PRESSURE activities will have access to any identifiable data. Following completion of the trial, all data will be anonymised.

ICNARC will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified to a third party without permission. Data will be stored in a secure manner and all of ICNARC CTU trials and studies are carried out in accordance with the Data Protection Act 2018. Any data leaving the NHS will be sent securely.

Conflicts of Interest

None.

Use of tissue samples in future research

None.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

In critically ill children with low blood pressure who are mechanically ventilated in intensive care, is a permissive (lower) blood pressure target, in order to minimise dose and duration of medical interventions, of benefit when compared to usual care?

Benefit will be defined in terms of the primary outcome measures of the trial, which will include measures of clinical and cost effectiveness.

The primary clinical effectiveness measure will be composite of mortality and duration of ventilator support, from

randomisation to day 30. The primary cost-effectiveness measure will be incremental net monetary benefit (INB), evaluated at the NICE recommended threshold of £20,000 per quality-adjusted life year (QALY), at 90 days.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

Secondary outcome measures will be
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 between PICU admission and PICU discharge, measured by the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales.
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 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). These are questionnaires used to assess quality of life in children.
Incremental costs at 30 days.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

In critically ill children, hypotension (low blood pressure) is common, especially in patients with severe infections. It is a key feature of shock. Untreated, hypotension compromises tissue perfusion and organ function, with an increased risk of multiple organ failure. Vasoactive agents (drugs which increase blood pressure by making blood vessels constrict and which also stimulate the heart) and fluid bolus therapy (a large volume of intravenous fluid given quickly and at one time) are mainstays of treatment. Around 80% of the 20,000 children admitted to UK PICUs each year receive fluid bolus therapy and around 30% receive vasoactive drugs at some point during their intensive care stay.

Though interventions to treat hypotension may be lifesaving, there are also harms. Excessive fluids are associated with prolonged PICU stay and increased morbidity and mortality. Most vasoactive drugs induce vasoconstriction, which may reduce blood flow and cause other secondary effects on organ function. Central venous catheters (tubes going into large veins) are usually sited to administer vasoactive drugs; these catheters are associated with an increased risk of thrombosis and infection, particularly in very small children.

Current guidelines recommend maintaining mean arterial pressure (MAP – mean arterial or average blood pressure) for children with severe infection and a number of other conditions around the 50th centile for age. Yet, these guidelines are based on low quality evidence and no guidance is given for an upper MAP limit.

In adults with critical illness, the 5th centile value for mean blood pressure has been recommended. This strategy has been examined in a number of recent randomised controlled trials, including SEPSISPAM, OVATION and 65, all of which investigated a permissive blood pressure target in critically ill adults with a variety of pathology. None of these studies demonstrated any significant difference in overall mortality between the lower and higher blood pressure target groups. However, a pooled analysis of SEPSISPAM and OVATION found an increased incidence of supraventricular tachycardia in the higher blood pressure target group and increased mortality in those patients in the higher blood pressure target group enrolled after > 6 h of vasopressors.

The PRESSURE trial will test the hypothesis that the benefits associated with a lower blood pressure target in critically ill children will outweigh the risks associated with lower MAP values and the medical interventions needed to raise blood pressure, improving outcomes and decreasing costs.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

PRESSURE is a multiple centre, randomised clinical trial (RCT). A RCT design was chosen as this is the gold standard design for clinical trials.

There are many treatments used in intensive care to treat low blood pressure, which include vasoactive drugs that make the heart pump faster, but these medical interventions carry risks. PRESSURE aims to identify the best blood pressure target in critically ill children to improve outcomes by minimising dose and duration of medical interventions, with the hypothesis that a lower blood pressure target is of significant benefit when compared to the higher targets used in current usual care. The null hypothesis would be that there is significant difference between the specified populations, any observed difference being due to sampling or experimental error.

We will recruit 1900 patients from 17 paediatric critical care units and their associated specialist retrieval services (teams of doctors and nurses that attend local hospitals to assist with the specialist care of critically ill children and their ambulance transportation to a regional, specialist paediatric intensive care unit). PRESSURE aims to start recruitment August 2021.

The study will use a deferred consent model due to the emergency nature of the patient population. Eligible patients will be randomised by the PICU or the retrieval teams and their parents or legal guardians will be approached for consent to continue in the study at the earliest appropriate opportunity (see section A6-2 for further details). Study participants will then be provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate. Parents/legal representatives will be involved in this discussion. In all other respects, the assenting procedures will follow the consenting procedures as described above.

The Participant Information Sheet (PIS) for parents/legal representatives will fully inform parents/legal representatives of what the research entails in clear, patient friendly language. It will also provide information on the completing a follow up questionnaire. Parents/Legal representatives will be given the opportunity to ask questions and to discuss the study with family or friends before making their decision. After the authorised staff member is satisfied that the PIS has been read and understood, and any questions have been adequately answered, only then will parents/legal representatives be invited to sign the Consent Form.

Whilst mortality is the most important outcome measure, it is challenging to adequately power a study on mortality alone within paediatrics. We will therefore use a combination of mortality (worst possible outcome) and days on mechanical ventilation as our primary outcome. We have used information from qualitative work to inform a composite outcome. This work highlighted the child 'looking and feeling more like themselves' and 'time on machines' as the most important outcome measures for parents.

Children will only be considered for the study if they (inclusion criteria):
• Age more than 37 weeks corrected gestational age and less than 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

Children with the following will not be recruited to the study (exclusion criteria):
• Admitted post cardiac surgery
• Known cardiomyopathy
• Neonates with suspected or proven duct dependent circulation
• Brain injury
• Pulmonary hypertension
• Malignant hypertension
• Death is perceived as imminent
• Recruited to PRESSURE in a previous admission

Once recruitment is completed, an equal number of children will have been allocated to each treatment group:

Intervention group:
Participants allocated to the intervention group will be treated using an allocated lower blood pressure target whilst receiving vasoactive drugs. The target allocated will depend on the participant's age. The decision to discontinue vasoactive drugs will depend on the patient's ability to maintain the target.

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

Usual care:
Participants allocated to this group will receive usual care, according to local practice.

Timetable
The sample size is 1900 patients. These patients will be recruited from 17 paediatric critical and intensive care units (PICUs) and associated PICU retrieval services over a 30-month recruitment period.

Data will be collected daily whilst in PICU to describe the intensity and duration of treatment, alongside routine data collection. Patients will be followed up after one year by postal questionnaire to ascertain their quality of life.

Statistical analysis
Following the end of recruitment, analysis of the study data will take place and articles will be prepared for publication. It will not be possible to identify any participants in any publications.

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.

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.

A single interim analysis will be undertaken following recruitment and follow-up to 30 days of 50% of patients to decide on early termination of the study due to either benefit or harm.

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 (the national PICU audit). PICANet will provide routine data on the level of care for PICU bed-days through collection of the data on intensive care interventions; this can be cross referenced to the Case Report Form (CRF) if necessary. 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 these questionnaires at 12 months will be combined with survival data to report Quality Adjusted Life Years (QALYs).

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

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
Patient, carer and public involvement and engagement is at the heart of ICNARC with two Trustees being ex-intensive care patients. In addition, our study team have experience leading research in a paediatric population including extensive experience of integrating their patient/parent group into their research to ensure their views are at the forefront of any study.

We have had extensive PPI input both into this proposal to ensure acceptability and applicability to parents, and, in addition, through our PPI work on other studies in this setting. These works have been vital to shape many aspects of this application and will be key to ensuring patients remain at the heart of the study.

Experience from other studies in the area informed the proposed choice of outcome measure. This was selected following work with families and parents in our recent Fluids in Shock and Fever pilot trials. Three out of the top four outcomes prioritised by parents were: improvement in organ and physiological function; ‘how quickly my child looks

like themselves again'; and reduced need/time spent on treatments and mechanical support. This feedback was crucial in the inclusion of duration of ventilator support in the composite outcome measure.

PPI involvement will be included in the day-to-day management of the trial. Co-applicant, DS, reviewed the application and he will continue to be an active member of the Trial Management Group throughout the course of the trial. In addition to our PPI co-applicant, our close ties with the GOSH patient group will mean we can access a wider group of patients/parents, this will be essential throughout, but especially during the dissemination process to ensure we are actively reporting the results (including study progress) to patients and parents in the most accessible format.

Patient/parent representatives, independent of the trial team, will be invited to join the TSC. The ICNARC CTU, using its extensive prior experience of PPI involvement, both as co-applicants and independent governance committee members on research studies, provides one-to-one training based on individual needs.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☐ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☑ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory
- ☐ Skin
- ☐ Stroke

Gender:	Male and female participants
Lower age limit: 37	Weeks gestational age
Upper age limit: 15	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

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

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

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

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Seeking informed consent from families	1		1 hour	This will be carried out by the local PRESSURE team (e.g. Principal Investigator, consultant or research nurse with prior experience of deferred consent or specific training from the PRESSURE team)
Completion of the one-year follow-up questionnaire assessing health-related quality of life and health service resource use	1		15 mins	Questionnaire centrally administered by a trained member of the PRESSURE study team at ICNARC CTU
Seeking informed assent	1		1 hour	If the participant's age and condition allows, assent will be carried out by the local PRESSURE research team in hospital as authorised on the PRESSURE delegation log.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).

4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Vasoactive drugs	1	1	dependent on need	To be delivered as per the protocol by trained clinical staff and expected to continue for at least 6 hours. The decision to discontinue vasoactive agents will be determined by the patients' ability to maintain the Mean Arterial Pressure target independently of support.
Permissive blood pressure target	1	1	dependent on need	To be delivered as per the protocol by trained clinical staff. The permissive blood pressure target will be allocated, based on age, at randomisation and should be followed at any point the patient needs vasoactive agents during the critical care unit admission.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

Each participant will, with consent, be followed up 1 year post-randomisation.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Clinical risks and burdens are not in excess of those normally applicable to patients in PICU as the blood pressure target in the permissive group is within the range of normal clinical practice. Patients with diagnoses which might put them at higher risk from a lower blood pressure target, e.g. traumatic brain injury, have been excluded from the trial.

Using a deferred consent process is a potential risk, as children may be entered into a study which could be against the wishes of the parents/legal representatives. We have minimised these risks by following the procedures as specified after the FiSh Feasibility Study (REC: 15/NW/0913; IRAS: 191348) in order to incorporate the wishes of parents/legal representatives. This took guidance from previous work in the area (by Dr Kerry Woolfall) and interviews with 21 parents (7 bereaved) whose child had been admitted to PICUs. Using these approved procedures minimises this potential risk.

In regards to the interviews and questionnaires, there is no foreseeable risk to parents/legal representatives. However, due to the emotive topic (critically ill children), there is a slight risk that the research may be burdensome. Therefore a number of steps have been taken to help minimise potential burden. The PRESSURE study team are experienced in the design and conduct of interviews with vulnerable groups on emotive topics; therefore all questions and prompts will be designed with the aim of reducing stress or personal intrusion. Parents/legal representatives will be free to withdraw from the study at any time without giving a reason. A list of appropriate referral agencies will be available if the parent/legal representative becomes upset.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◉ Yes ○ No

If Yes, please give details of procedures in place to deal with these issues:

Questionnaires on quality of life have the possibility to cause some stress as they may draw parents' attention to any changes and act as a reminder of the child's PICU admission. However, the critical care community is increasingly aware that critical care admission may be associated with long-term deficits. In order to fully understand the efficacy of each treatment arm, we must understand the patient's subsequent experience. Previous research suggests that

participants appreciate the opportunity to express how their child's PICU stay affected their lives. Parents will not be pressured or coerced into completing the questionnaire and it will be their decision whether or not to complete it.

A24. What is the potential for benefit to research participants?

No promises will be made to participants. They may be allocated to the intervention which may have a benefit associated with lower blood pressure targets and thereby less medical interventions needing to raise blood pressure. Knowledge generated will benefit critically ill children treated in PICU which we know from previous work is a big driver of research participation within PICU.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Not applicable. The intervention will be provided to the patient for the period that they are in the PICU.

A26. What are the potential risks for the researchers themselves? *(if any)*

None

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

All potential participants will be identified and screened for eligibility by the trained research and clinical teams on the PICU or by PICU retrieval teams. Identifiable data will only be accessed by the direct care team, who generally have dual clinical and research roles. They will assess if the patient meets all the inclusion criteria and none of the exclusion criteria, based on their presentation, medical history and clinical notes. All admissions will to the PICU will be logged on the PRESSURE screening and enrolment log at each site.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
Identifiable patient data will be reviewed/screened by local NHS staff to assess eligibility. These staff are part of the direct care team who have dual clinical and research roles and will be directly caring for the patients on PRESSURE and administering the intervention where applicable.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Patient data which may be identifiable will only be reviewed/screened by the local direct healthcare team working on the trial (local PRESSURE team). All staff confirming eligibility will be required to be entered onto the PRESSURE

delegation log and approved by the site PI. No identifiable information will be passed to any individual outside of the local PRESSURE team until the parents/legal representatives of the patient have consented to participate. All sites will undergo a site initiation meeting where the importance of confidentiality will be outlined.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The clinical/research team will prospectively identify eligible patients based on the inclusion criteria and follow the consent procedures outlined in section A6-2.

Parents/legal guardians will only be approached as soon as practically and appropriately possible by authorised staff members who have received training in trial processes and procedures and in Good Clinical Practice (GCP). The recruitment process will be done in such a way as to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

Due to age and severity of illness, it is unlikely study participants will be involved in this process. Instead, assent will be obtained prior to hospital discharge if their condition allows. Study participants will also be provided with an age-appropriate PIS and they will be asked to confirm they have been informed and understand the study. Parents/legal guardians will be involved in this discussion.

If the participant has died prior to their parents/legal representatives or potential participant being approached, then one of the hospital's local PRESSURE team (a member of the healthcare team) will obtain information from colleagues and bereavement counsellors to establish the most appropriate staff member to notify parents/legal representatives of the involvement in the research study. In this situation, parents/legal representatives can be approached either prior to their departure from the hospital or by post four weeks after randomisation. However, it is at the discretion of the staff to determine the most appropriate time to be approached for each individual family.

In the unlikely situation where a participant is discharged from hospital before consent has been sought, one of the hospital's local PRESSURE team (a member of the healthcare team) will attempt at least one phone call to the parents/legal
representatives within five working days of discharge to inform them of the participant’s involvement in the study and provide details of the study. Following on from the call, as well as if there is no response to the call, the parents/legal representatives 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.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

We will obtain consent after randomisation, using a deferred consent model employed in a number of paediatric critical care clinical trials. We believe that this is the only appropriate model for consent in this critical care setting.

Parents/Legal representatives, or when applicable, the research participant, will be provided with written information about the study and supplemented with information provided orally. They will be given a copy of the PIS, which includes information about: the purpose of the study; how the study is being funded; the consequences of

participating or not; participant confidentiality; data security; and the future availability of the results of the study. It will also provide information on the completing the optional follow up questionnaire. The contact details for the local PI will be included on the PIS.

Parents/Legal representatives, or where applicable, the research participant, will be given the opportunity to ask questions and to discuss the study with family or friends before making their decision.

After the authorised staff member is satisfied that the PIS has been read and understood, and any questions have been adequately answered, parents/legal representatives will be invited to sign the Consent Form. A copy of the signed Consent Form will be given to the parent/legal representative, a copy placed in the patient's medical notes and the original kept in the Investigator Site File (ISF) at the hospital.

Study participants will then be provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate. Parents/legal representatives will be involved in this discussion. In all other respects, the assenting procedures will follow the consenting procedures as described above.

In a situation where a participant dies before consent has been sought, consent will be sought either prior to the parents/legal representative's departure from the hospital or by post four weeks after randomisation. If parents/legal representatives are approached in hospital, then they will go through the same consenting procedures as above. They will be given a PIS specifically for bereaved parents/legal representatives. From experience in previous studies, it may be very difficult to approach parents/legal representatives prior to departure from the hospital.

If the parents/legal representatives are not approached in hospital, then they will be sent a covering letter, personalised by the most appropriate healthcare practitioner in the clinical team, and a copy of the PIS specifically for bereaved parents/legal representatives and Consent Form (postal version for bereaved parents/legal representatives) by post four weeks after randomisation. The letter will explain how to opt out of the study, direct them to the PIS for detailed information on the study and provide telephone contact details if parents/legal representatives wish to discuss the study with a member of the research team. The PIS will explain that even if consent is refused, a minimised anonymised dataset will be retained, due to the importance of monitoring both safety and the primary outcome, but that no additional information will be collected. If there is no response after four weeks of sending the initial letter, a follow-up letter, along with the same study documentation as before, will be sent. 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 unless the family notify the site team otherwise.

In the unlikely situation where a participant is discharged from hospital before consent has been sought, the parents/legal representatives will be called and then sent a covering letter, personalised by the most appropriate healthcare practitioner in the clinical team, and a copy of the PIS and Consent Form (postal version) by post. The letter will explain how to opt out of the study, direct them to the information sheet for detailed information on the study and provide telephone contact details if parents/legal representatives 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 same study documentation as before, will be sent. 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 unless the family notify the site research team otherwise.

Further details are provided in section A6-2.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

Parents/guardians of critically ill children will be given as long as they require to read the information sheet and ask questions. Only after they have fully understood the study would they be asked to sign the consent form.

The principal advantage of the 'deferred consent' or 'research without prior consent' approach is that families have

time to consider the information and to discuss with wider family, friends, and clinical and research staff without the immediate time pressure of the intervention awaiting their decision.

In practice, we will typically approach the family the day after ICU admission and seek to obtain consent within 24-48 hours.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- (●) Yes
- ( ) No
- ( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

We will include children who may be part of research protocols as a result of acute or chronic diseases that are not directly related to the need for intensive care. With respect to PICU studies, the research team will consider co-enrolment of PRESSURE participants onto other interventional studies where the management does not conflict with the trial's objectives on a case-by-case basis

Participants will be permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies). We will follow the "CO-ENROLMENT TO CRITICAL CARE STUDIES AND TRIALS IN THE UNITED KINGDOM" guidance document from 2012 produced by the Intensive Care Society. Co-enrolment agreements will be put in place on a case-by-case basis. Details of any co-enrolment will be documented on the PRESSURE study Case Report Form.

In practice this is not an issue; because of the highly coordinated approach to paediatric intensive care research, we are aware of the other protocols that may be relevant. All such studies are delivered in each centre by a common team of research doctors and nurses.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

If the parents/legal representatives or potential participants do not understand oral or written information in English, translation services will be used as per routine practice at each of the participating sites. Despite use of interpreters to explain the study procedure, if there is uncertainty among the research team whether parents/legal representatives have fully understood the study, the patient will be excluded from the study.

For the follow up questionnaire, as we are unable to conduct interviews in any languages other than English, we are unable to include participants who do not speak English.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

All participating hospitals in Wales will have access to a Welsh translator.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The Chief Investigator will inform both the Trial Steering Committee and the Data Monitoring & Ethics Committee of any relevant new data if it appears.

All information received of any importance will be passed on through the PI at the site.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

○ The participant would continue to be included in the study.

◉ Not applicable – informed consent will not be sought from any participants in this research.

○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:
Consent for patient's participation will be gained from parents who are not expected to have fluctuations in capacity.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☑ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☑ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☐ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:
Members of the PRESSURE team from the ICNARC CTU will require access to the patient's medical notes during routine trial monitoring visits conducted at the hospital to ensure the quality of the data collection and consent procedures.

Identifiable data (name and contact details) will be sent to and stored at ICNARC CTU to enable a follow up questionnaire to be sent to the parents of recruited patients (as long as they consent to this). 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. In addition, further identifiable data (name, date of birth, NHS number) will be

required to enable linkage with NHS Digital (or equivalent) for trial outcome data (mortality), (parents will also consent to this). All data will be encrypted to an appropriate standard prior to transfer from the hospital.

The PI and delegated members of the local research team will have access to the link code for the identifying data. ICNARC will also hold the link code for participants for whom consent for follow-up is in place.

Storage of personal data:
All data will be appropriately filed and securely stored in a locked cabinet or in an encrypted electronic file.

All NHS computers will only be accessible to authorised staff with the correct access control permissions.

All ICNARC CTU computers will only be accessible by password access to authorised staff with the correct access control permissions.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal data (e.g. name of child, NHS number, date of birth, name of parent/legal guardian) will need to be sent to and stored at ICNARC CTU to enable a follow-up questionnaire to be sent to the parents/legal guardian and to obtain data from NHS Digital (or their equivalent).

At the ICNARC CTU, personal data is collected on a secure web-based data entry system housed at Exponential-E (a third-party contractor providing services to ICNARC). Exponential-E is a specialist hosting provider and all data centre buildings include proximity access control and digital CCTV to control physical access to equipment. ICNARC has assessed this supplier as low risk and this is acceptable to ICNARC

With regards to the ICNARC office based in London, England - physical office security includes a Grade 3 Red Care intruder detection system that has been supplied, installed and is maintained by ADT Fire and Security Plc. All visitors are notified to building security by ICNARC staff in advance.

Participant questionnaires received are identified by a unique study reference number. These are stored in locked cupboards, restricted to authorised staff only. Data destruction will be carried out in compliance with the UK Policy Framework for Health and Social Care Research and we work with suitably qualified contractors for both electronic and paper record destruction.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

To minimise the use of personal identifiers, participants will be allocated a unique Trial Number and this will be used by the study team in communications with the local research teams at participating sites.

ICNARC and the local NHS Trust will hold the link code.

Personal data will only be processed in physical form where absolutely necessary (e.g. when posting a letter to a parent/guardian).

ICNARC is registered under the Data Protection Act (Registration number: Z6289325). Confidentiality forms the basis of ICNARC's Information Security Policy. All staff employed by ICNARC sign a contract, which incorporates a confidentiality clause and the consequences of breaching confidentiality are covered in our Disciplinary Procedure. External researchers, temporary staff and contractors are all required to sign a formal confidentiality agreement with ICNARC. Data security and confidentiality are a fixed agenda item at staff meetings for all staff at ICNARC.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participant data will be held on a secure web-based data entry system. Access to the secure web-based data entry system in the hospitals will be restricted (by username and password) to trained staff in the hospital, authorised by the site Principal Investigator. Patients' identification data, including full name, date of birth, full address and NHS number, will be required at ICNARC. It is necessary to collect this identifiable information as follow-up questionnaires need to be sent directly to the parent/legal representative. ICNARC will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients or their parent/legal representative could be identified to a third party.

Data will be stored in a secure manner and ICNARC are registered in accordance with the Data Protection Act 2018.

Access to participant's personal data will be limited to authorised staff members at the ICNARC CTU (the PRESSURE trial team). The site Principal Investigators will take responsibility for ensuring that study data stored on paper at the site is restricted to authorised personnel only (as per the Delegation Log).

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data generated by the PRESSURE study will be analysed by appropriately qualified members of the PRESSURE study team within the ICNARC office in London, England.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Dr	David	Inwald
Post	Consultant in Paediatric Intensive Care		
Qualifications	MBBChir FRCPCH FFICM PhD		
Work Address	Cambridge University Hospitals NHS Trust		
	PICU Addenbrooke's Hospital		
	Cambridge		
Post Code	CB2 0QQ		
Work Email	di260@cam.ac.uk		
Work Telephone	0791737389		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
Identifiable data will be kept for up to one year after the study has ended. If parents/legal guardians agree to be contacted about future research studies (the final point on the Consent Forms), their identifiable data will be kept for five years after the end of the study for this purpose.

A44. For how long will you store research data generated by the study?

Years: 10
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

In line with Standard Operating Procedures (SOPs) for ICNARC CTU, all central essential documents will be archived for 10 years after the end of the trial. Once this period has passed, arrangements will be made for its confidential destruction.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The research will be registered with the ISRCTN Registry and NIHR Clinical Research Network Portfolio

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication

☐ Submission to regulatory authorities

☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators

☐ No plans to report or disseminate the results

☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

It will not be possible to identify any person who has taken part in the study in any reports or articles. Any identifiable personal data will be anonymised following completion of participant follow-up.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.
Results will be disseminated to those hospitals who participated in the study, and summarised on the ICNARC website. Participants and their parents/legal representatives will be informed in the PIS as to where they can access results of the study.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

☑ Independent external review

☐ Review within a company

☐ Review within a multi−centre research group

☐ Review within the Chief Investigator's institution or host organisation

☑ Review within the research team

☐ Review by educational supervisor

☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The PRESSURE study has been reviewed by the Paediatric Intensive Care Society Study Group (PICS-SG). It has also been reviewed extensively by the NIHR Health Technology Assessment (HTA) programme which commissioned the trial. The review included anonymous review by an independent statistician.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☑ Review by independent statistician commissioned by funder or sponsor

☐ Other review by independent statistician

☐ Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☑ Review by a statistician within the research team or multi−centre group

☐ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
		Anonymous	Reviewer
Department	Health Technology Assessment (HTA) Programme		
Institution	National Institute of Health Research (NIHR)		
Work Address			
Post Code			
Telephone			
Fax			
Mobile			
E-mail			

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

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

A58. What are the secondary outcome measures?*(if any)*

• 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 between PICU admission and PICU discharge, measured by the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales.

• 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)

• Incremental costs at 30 days

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 1900

Total international sample size (including UK):
Total in European Economic Area:

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

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.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of 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.

PRESSURE permissive MAP targets (lower-upper permissive PRESSURE target)

	Lower target	Upper target
Less than 1 year	35	40
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

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

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. 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.

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.

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. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Professor	Kathryn	Rowan
Post	Director of Scientific and Strategic Development		
Qualifications	PhD, MSc, BSc		
Employer	ICNARC		
Work Address	Napier House 24 High Holborn		
Post Code	WC1V 6AZ		
Telephone	02072699277		
Fax			
Mobile			
Work Email	kathy.rowan@icnarc.org		

	Title	Forename/Initials	Surname
	Mr	Paul	Mouncey
Post	Head of Research		
Qualifications	MSc		
Employer	ICNARC		
Work Address	Napier House 24 High Holborn		
Post Code	WC1V 6AZ		
Telephone	02072699277		
Fax			
Mobile			
Work Email	paul.mouncey@icnarc.org		

	Title	Forename/Initials	Surname
	Ms	Alanna	Brown
Post	Trial Manager		
Qualifications	BSc MSc		
Employer	ICNARC		
Work Address	Napier House 24 High Holborn		

Post Code	WC1V 6AZ
Telephone	020 4513 6248
Fax	
Mobile	
Work Email	alanna.brown@icnarc.org

Title	Forename/Initials	Surname
Professor	David	Harrison

Post	Head Statistician
Qualifications	PhD, MA, BA
Employer	ICNARC
Work Address	Napier House 24 High Holborn
Post Code	WC1V 6AZ
Telephone	02072699277
Fax	
Mobile	
Work Email	david.harrison@icnarc.org

Title	Forename/Initials	Surname
Associate Professor	Joseph	Manning

Post	Associate Professor of Nursing
Qualifications	PhD
Employer	Nottingham University
Work Address	
Post Code	
Telephone	
Fax	
Mobile	
Work Email	joseph.manning@nottingham.ac.uk

Title	Forename/Initials	Surname
Professor	Mark	Peters

Post	Professor of Paediatric Intensive Care Medicine
Qualifications	MB BS, FRCPCH, PhD
Employer	University College London
Work Address	Institute of Child Health 30 Guilford Street London
Post Code	WC1N 1EH
Telephone	02074059200
Fax	
Mobile	
Work Email	mark.peters@ucl.ac.uk

	Title	Forename/Initials	Surname
	Dr	Samiran	Ray
Post	Consultant in Paediatric Intensive Care		
Qualifications	MA, MB BChir, MRCPCH, PhD		
Employer	Great Ormond Street Hospital for Children NHS Trust		
Work Address	Great Ormond Street London		
Post Code	WC1N 3JH		
Telephone	02074059200		
Fax			
Mobile			
Work Email	samiran.ray@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Associate Professor	Padmanabhan	Ramnarayan
Post	Consultant in Paediatric Intensive Care		
Qualifications	MB ChB, FRCPCH, MD		
Employer	Great Ormond Street Hospital for Children NHS Trust		
Work Address	Children's Acute Transport Service London		
Post Code	WC1N 3JH		
Telephone	02074305850		
Fax			
Mobile			
Work Email	p.ramnarayan@gosh.nhs.uk		

	Title	Forename/Initials	Surname
	Dr	Zia	Sadique
Post	Assistant Professor in Health Economics		
Qualifications	PhD		
Employer	London School of Hygiene and Tropical Medicine (LSHTM)		
Work Address	Keppel Street London		
Post Code	WC1E 7HT		
Telephone	02076368636		
Fax			
Mobile			
Work Email	zia.sadique@lshtm.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Barney	Scholefield
Post	Consultant in Paediatric Intensive Care		
Qualifications	MB BS, MRCPCH, PhD		
Employer	Birmingham Children’s Hospital NHS Trust		
Work Address	Steelhouse Lane Birmingham		

Post Code	B4 6NH
Telephone	0121 333 9999
Fax	
Mobile	
Work Email	B.Scholefield@bham.ac.uk

Title	Forename/Initials	Surname
Mr	Dermot	Shortt

Post	PPI representative
Qualifications	BE (Elec Eng)
Employer	Finbourne
Work Address	The Frames 1 Phipp Street London
Post Code	EC2A 4PS
Telephone	02038828766
Fax	
Mobile	
Work Email	dermot@shortty.com

Title	Forename/Initials	Surname
Ms	Karen	Thomas

Post	Senior Statistician
Qualifications	BSc, MSc
Employer	ICNARC
Work Address	Napier House 24 High Holborn
Post Code	WC1V 6AZ
Telephone	02072699277
Fax	
Mobile	
Work Email	Karen.Thomas@icnarc.org

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	Cambridge University Hospital NHS Foundation Trust
Given name	Stephen
Family name	Kelleher
Address	Hills Road
Town/city	Cambridge
Post code	CB2 0QQ,
Country	United Kingdom
Telephone	01223 217418
Fax	01223 348494
E-mail	research@addenbrookes.nhs.uk

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	National Institute of Health Research (NIHR)
Address	Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House, Enterprise Road, Southampton
Post Code	SO16 7NS
Telephone	02380595586
Fax	02380595639
Mobile	
Email	hta.funding@nihr.ac.uk

Funding Application Status: (•) Secured ( ) In progress

Amount: 1,716,166.20

Duration
Years:
Months: 54

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
NIHR HTA programme

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

(●) Yes ( ) No

Name: Intensive Care National Audit and Research Centre

Type of organisation:
( ) NHS ( ) Academic ( ) Commercial (●) Other

Please give further details of sub-contractor and main areas of delegated responsibility:

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (●) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Mr	Adam	Loveday
Organisation	Cambridge University Hospitals NHS Foundation Trust		
Address	Hills Road		
	Cambridge		
Post Code	CB2 0QQ		
Work Email	adam.loveday@addenbrookes.nhs.uk		
Telephone	01223348455		
Fax	01223348455		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

Eastern

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 02/08/2021
Planned end date: 28/02/2025
Total duration:
Years: 3 Months: 6 Days: 27

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	13
☑ NHS organisations in Wales	1
☑ NHS organisations in Scotland	2
☑ HSC organisations in Northern Ireland	1
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	

☐ Independent (private or voluntary sector) organisations
☐ Educational establishments
☐ Independent research units
☐ Other (give details)

Total UK sites in study: 17

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Recruitment
The Chief Investigator will delegate recruitment of participants at the study research sites to the local PIs. This may be further delegated to local research nurses and investigators. Details of delegation will be recorded in delegation logs. The local PI will ensure adequate local training of all staff involved in the study.

Management
Management and monitoring of the study will be delegated by the study Sponsor to the ICNARC CTU. The progress of the study will be monitored and supervised by the SSC. At least 75% of the members will be independent (including the Chair). It will also consist of at least one service user representative, experienced paediatric emergency medicine and critical care clinicians and the Chief Investigator.

Central monitoring
The study team at the ICNARC Clinical Trials Unit will communicate regularly with sites via email, telephone, teleconferences and newsletters. Data recorded in the central, secured data entry system will undergo checks for accuracy, completeness and consistency. The local Principal Investigator will be responsible for ensuring all data queries are addressed and for the overall quality of local data. A particular emphasis will be put on adherence to the trial protocol.

Site monitoring
The site monitoring plan will be based on a risk assessment, including an assessment of the sites and local research team (e.g. experience of multi-centre research, RCTs, etc.). Sites will be visited based on a risk assessment model to monitor and discuss adherence to the trial protocol and standard operating procedures. Directly following all site visits, the site PI will be verbally advised of the core monitoring findings and this will be followed with a written report to the site summarising the visit, documents reviewed and any findings. Information learnt at site visits will be used to refine standard operating procedures, as required, ensuring clarity and consistency across sites.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

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.

In line with Standard Operating Procedures at the ICNARC CTU, a Data Monitoring and Ethics Committee (DMEC) will be convened and will include experienced critical care clinicians and at least one statistician. All members of the DMEC will be independent of both the trial and the Trial Steering Committee (TSC), and will operate under the DAMOCLES Charter. The DMEC will report to the TSC, making recommendations on the continuation, or not, of the study. Adherence to the intervention and safety will be monitored by the DMEC throughout the study period.

In addition to this the DMEC will meet at least once and year and review line listings of serious adverse events at each meeting

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive

summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

Interim analysis will use 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).

An internal pilot phase which will run for six months (months 7-12) and will assess key progression criteria using a traffic light system. Key progression criteria will include: site opening; patient recruitment; and separation between the groups. The same processes, as the main RCT, will be used throughout the internal pilot phase, with all patients recruited in the six-month period included in the final analysis.

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.

A Data Monitoring and Ethics Committee (DMEC) will be convened and will include experienced paediatric emergency medicine and critical care clinicians and statistician. All members of the DMEC will be independent of both the study and TSC, and will operate under the DAMOCLES charter. The DMEC will report to the TSC, making recommendations on the continuation, or not, of the study. Adherence to the intervention and safety will be monitored by the DMEC throughout the study period.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ○ No ◉ Not sure

PART B: Section 7 - Children

1. Please specify the potential age range of children under 16 who will be included and give reasons for carrying out the research in this age group.

37 weeks completed gestational age <16 years. This study is being conducted in this age range because this is the population in which we have identified the uncertainty with regard to the optimal blood pressure target.

2. Indicate whether any children under 16 will be recruited as controls and give further details.

Yes - the same patient population will be included in both of the parallel groups.

3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.

We are planning a 'deferred consent' or 'research without prior consent' model as has been successfully used in recent and current studies in paediatric critical care and paediatric emergency medicine.

Parents/legal representatives will be provided with written information about the study supplemented with information provided orally. They will be given a copy of the PIS, which includes information about: the purpose of the study; how the study is being funded; the consequences of participating or not; participant confidentiality; data security; and the future availability of the results of the study. It will also provide information on completing the optional questionnaire. The contact details for the local PI will be included on the PIS. Parents/Legal representatives will be given the opportunity to ask questions and to discuss the study with family or friends before making their decision. After the authorised staff member is satisfied that the PIS has been read and understood, and any questions have been adequately answered, parents/legal representatives will be invited to sign the Consent Form. Once they have signed the Consent Form, the person taking informed consent will add their own name and countersign in the presence of the parent/legal representative. A copy of the signed Consent Form will be given to the parent/legal representative, a copy placed in the patient's medical notes, and the original kept in the ISF at the hospital.

In a situation where a participant dies before consent has been sought, consent will be sought either prior to the parents'/legal representatives' departure from the hospital or by post four weeks after randomisation. If parents/legal representatives are approached in the hospital, they will go through the same consenting procedures as above. They will be given a PIS specifically for bereaved parents/legal representatives. If, following the death of a participant, the

parents/legal representatives are not approached in the hospital, they will be sent a covering letter, personalised by the most appropriate healthcare practitioner in the clinical team, and a copy of the PIS. A follow-up letter will be sent if there is no response and an opt-out option given.

4. If you intend to provide children under 16 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.

We have produced age appropriate information sheets for children under 8, 8-10 years and 11 years and up. Research staff are very experienced in talking to children in the aftermath of serious illness including explaining how trials and randomisation work. If the child reaches their 16th birthday whilst on the study (during PICU stay) we do not intend to obtain an additional consent from the patient.

Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Rebecca Mitting r.mitting@nhs.net
	Organisation name	IMPERIAL COLLEGE HEALTHCARE NHS TRUST	Qualification (MD...)	
	Address	THE BAYS ST MARYS HOSPITAL SOUTH WHARF ROAD LONDON	Country	
	Post Code	W2 1BL		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Pompa Kukreja pompa.kukreja@uhl-tr.nhs.uk
	Organisation name	UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST	Qualification (MD...)	
	Address	LEICESTER ROYAL INFIRMARY INFIRMARY SQUARE LEICESTER	Country	
	Post Code	LE1 5WW		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Adeyemisi Jegede ajegede@nhs.net
	Organisation name	KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST	Qualification (MD...)	
	Address	DENMARK HILL LONDON	Country	
	Post Code	SE5 9RS		

Country	ENGLAND

IN4

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	JOHN RADCLIFFE HOSPITAL HEADLEY WAY HEADINGTON OXFORD
Post Code	OX3 9DU
Country	ENGLAND

Forename	Avishay
Middle name	
Family name	Sarfatti
Email	avishary.sarfatti@ouh.nhs.uk
Qualification (MD...)	
Country	

IN5

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS BRISTOL AND WESTON NHS FOUNDATION TRUST
Address	TRUST HEADQUARTERS MARLBOROUGH STREET BRISTOL
Post Code	BS1 3NU
Country	ENGLAND

Forename	Alvin
Middle name	
Family name	Schadenberg
Email	Alvin.Schadenberg@uhbw.nhs.uk
Qualification (MD...)	
Country	

IN6

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	NHS Greater Glasgow and Clyde
Address	J B Russell House Gartnavel Royal Hospital 1055 Great Western Road Glasgow Glasgow Scotland
Post Code	G12 0XH
Country	SCOTLAND

Forename	Alastair
Middle name	
Family name	Turner
Email	Alastair.turner@ggc.scot.nhs.uk
Qualification (MD...)	
Country	

IN7

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	LEEDS TEACHING HOSPITALS NHS TRUST
Address	ST. JAMES'S UNIVERSITY HOSPITAL BECKETT STREET LEEDS
Post Code	LS9 7TF
Country	ENGLAND

Forename	Assaf
Middle name	
Family name	Doulah
Email	assafdoulah@nhs.net
Qualification (MD...)	
Country	

IN8

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	ALDER HEY CHILDREN'S NHS FOUNDATION TRUST
Address	ALDER HEY HOSPITAL EATON ROAD WEST DERBY LIVERPOOL
Post Code	L12 2AP
Country	ENGLAND

Forename	Ben
Middle name	
Family name	Lakin
Email	ben.lakin@alderhey.nhs.uk
Qualification (MD...)	
Country	

IN9

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	MANCHESTER UNIVERSITY NHS FOUNDATION TRUST
Address	COBBETT HOUSE OXFORD ROAD MANCHESTER
Post Code	M13 9WL
Country	ENGLAND

Forename	Ravishankar
Middle name	
Family name	Nagaraj
Email	ravishankar.nagaraj@mft.nhs.uk
Qualification (MD...)	
Country	

IN10

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	CAMBRIDGE UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	CAMBRIDGE BIOMEDICAL CAMPUS HILLS ROAD CAMBRIDGE
Post Code	CB2 0QQ
Country	ENGLAND

Forename	David
Middle name	
Family name	Inwald
Email	david.inwald@addenbrookes.nhs.uk
Qualification (MD...)	
Country	

IN11

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	BARTS HEALTH NHS TRUST
Address	THE ROYAL LONDON HOSPITAL 80 NEWARK STREET LONDON
Post Code	E1 2ES
Country	ENGLAND

Forename	Simona
Middle name	
Family name	Lampariello
Email	s.lampariello@nhs.net
Qualification (MD...)	
Country	

IN12

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS OF NORTH MIDLANDS NHS TRUST
Address	NEWCASTLE ROAD STOKE-ON-TRENT
Post Code	ST4 6QG
Country	ENGLAND

Forename	John
Middle name	
Family name	Alexander
Email	john.alexander@uhnm.nhs.uk
Qualification (MD...)	
Country	

IN14

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	SHEFFIELD CHILDREN'S NHS FOUNDATION TRUST
Address	WESTERN BANK SHEFFIELD
Post Code	S10 2TH
Country	ENGLAND

Forename	Anton
Middle name	
Family name	Mayer
Email	anton.mayer@nhs.net
Qualification (MD...)	
Country	

IN15

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST
Address	TRUST HEADQUARTERS QUEENS MEDICAL CENTRE DERBY ROAD NOTTINGHAM
Post Code	NG7 2UH
Country	ENGLAND

Forename	Shrirang
Middle name	
Family name	Alurkar
Email	shrirang.alurkar@nuh.nhs.uk
Qualification (MD...)	
Country	

IN16

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST
Address	FREEMAN HOSPITAL FREEMAN ROAD HIGH HEATON NEWCASTLE UPON TYNE
Post Code	NE7 7DN
Country	ENGLAND

Forename	Rachel
Middle name	
Family name	Agbeko
Email	rachel.agbeko@nhs.uk
Qualification (MD...)	
Country	

IN17

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	GREAT ORMOND STREET HOSPITAL FOR CHILDREN NHS FOUNDATION TRUST
Address	GREAT ORMOND STREET LONDON
Post Code	WC1N 3JH
Country	ENGLAND

Forename	Mark
Middle name	
Family name	Peters
Email	mark.peters@ucl.ac.uk
Qualification (MD...)	
Country	

IN18

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	CARDIFF & VALE UNIVERSITY LHB
Address	WOODLAND HOUSE MAES-Y-COED ROAD CARDIFF
Post Code	CF14 4HH
Country	WALES

Forename	Selyf
Middle name	
Family name	Shapey
Email	selyf.shapey@wales.nhs.uk
Qualification (MD...)	
Country	

IN19

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITAL SOUTHAMPTON NHS FOUNDATION TRUST
Address	SOUTHAMPTON GENERAL HOSPITAL TREMONA ROAD SOUTHAMPTON
Post Code	SO16 6YD
Country	ENGLAND

Forename	Iain
Middle name	
Family name	Macintosh
Email	iain.macintosh@uhs.nhs.uk
Qualification (MD...)	
Country	

IN20

(●) NHS/HSC Site

( ) Non-NHS/HSC Site

Forename	Barney
Middle name	
Family name	Scholefield
Email	b.scholefield@bham.ac.uk
Qualification (MD...)	
Country	

Organisation name	BIRMINGHAM WOMEN'S AND CHILDREN'S NHS FOUNDATION TRUST
Address	STEELHOUSE LANE
	BIRMINGHAM WEST MIDLANDS
Post Code	B4 6NH
Country	ENGLAND

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr David Inwald on 05/03/2021 13:30.

Job Title/Post:	Consultant in Paediatric Intensive Care
Organisation:	Cambridge University Hospitals NHS Trust
Email:	di260@cam.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Dr Adam Loveday on 08/03/2021 14:00.

Job Title/Post:	Research Governance Coordinator
Organisation:	Cambridge University hospitals NHS Foundation Trust
Email:	adam.loveday@addenbrookes.nhs.uk