PRESSURE Trial FAQs

Screening and Eligibility

Can patients be included if they are admitted from theatre with vasoactives already commenced, and are deemed to have hypotension?

Yes, if the infusion was started within the last 6 hours and the clinical team believe the infusion will continue for more than 6 hours.

Can eligible patients be randomised in the Emergency Department if they have been accepted for admission to the paediatric critical care unit?

Yes, if they meet all eligibility criteria and the vasoactive infusion was started within the last 6 hours and the clinical team believe the infusion will continue for more than 6 hours.

Can retrieval teams randomise patients for PRESSURE?

Yes, if the patient meets all inclusion criteria, none of the exclusion criteria and the vasoactive infusion was started within the last 6 hours and they believe the infusion will continue for more than 6 hours. Also, if the patient has been accepted into a unit participating in the study.

A patient had 3 hours of vasoactives, then was off vasoactives for 6 hours and has now restarted, can they be included and when would the 6 hours recruitment window end?

The 6-hour eligibility period begins with the first infusion of a vasoactive, whether the vasoactives were administered within or outside the participating unit. Temporary interruptions do not push back the 6-hour mark. This patient would not be eligible.

If a patient is admitted to PICU but is not receiving vasoactives at the time of screening, can they be re-screening if they later commence on vasoactives?

Yes, if a patient is started on vasoactives later during PICU stay, site research team should re-screen.

Should all patient on vasoactives be screened?

Any patients accepted for / admitted to PICU and are receiving on vasoactives should be entered on the screening and enrolment log

Are tracheostomy ventilated patients eligible?

Yes, patients ventilated via tracheostomy can be included if they meet all other eligibility criteria.

Are patients currently enrolled on a different study eligible for recruitment?

The Trial Management Group will consider co-enrolment of PRESSURE participants onto other interventional studies on a case-by-case basis and we ask that you contact the PRESSURE team if you have any queries, and co-enrolment agreements will be put in place, as requested. Co enrolment(s) will be documented on the PRESSURE Trial Case Report Form. Participants are permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies).

Current agreed co-enrolments to PRESSRE:
BATCH trial.

Trials which cannot co-enrol to PRESSURE:
Oxy-PICU
PROSPECT

Our unit is also recruiting patients for Oxy-PICU,

- ***can we recruit patients both into Oxy-PICU and into PRESSURE?***

The Trial Management Group has determined that patients recruited for Oxy-PICU cannot be recruited into PRESSURE, and vice versa. Units involved in both studies are requested to preferentially consider eligibility for PRESSURE in patients **on** vasoactives and eligibility for Oxy-PICU in patients **not on** vasoactives.

- ***can we recruit a patient to PRESSURE if they have been in Oxy-PICU***

If an Oxy-PICU patient has been discharged and it is **more** than 30 days from randomisation since the readmission, they can be randomised to PRESSURE. If they are readmitted **within** 30 days of randomisation to Oxy-PICU they should return to the original Oxy-PICU treatment target and data collection should continue,

What do you mean by 'vasoactives are expected for at least 6 hours'?

The rationale for this inclusion criterion is to enrol patients who are on the sicker end of the spectrum. Therefore, we request that, when considering eligibility for PRESSURE, the person prescribing vasoactives believes that vasoactives will continue for 6 hours under usual circumstances. We will closely monitor the duration of vasoactive therapy in the usual care arm as few patients are expected to be off vasoactives within 6 hours of randomisation. In contrast, in the intervention arm, more patients will be off vasoactives within this time window as the intervention is aimed at reducing exposure to vasoactives.

Are patients admitted after/during a cardiac arrest eligible to participate?

In general, these patients would not be eligible for randomisation due to the high likelihood of brain injury in hypotensive post cardiac arrest patients. If the clinical team can rule out this contraindication (e.g. brief cardiac in-hospital arrest for whatever reason, or respiratory arrest, when acute brain injury is not suspected) the patient would be eligible.

Regarding the acute or evolving brain injury exclusion criterion – what does this cover?

Traumatic brain injury and any acute or evolving neurological condition requiring a neurointensive care strategy would be considered as exclusions. The rationale is that in these cases, management involves targeting a higher blood pressure than normal. However, if a patient had an acute neurological event a while ago and is in the ICU for some other reason, then it would be acceptable to enrol. If a patient is admitted with a neurological diagnosis but acute or evolving brain injury is not suspected, and they are not on a neurointensive care pathway (e.g. status epilepticus), the patient would be also eligible for the study.

What if a patient who had a brain injury previously, now develops septic shock after being discharged to the ward. Can they be included on readmission to ICU?

The exclusion criterion for brain injury is “acute or evolving” because treatment protocols are typically prescriptive with regards to blood pressure targets in these patients. Having suffered a brain injury in the past is not an exclusion criterion. In the event of a recent injury (e.g. during the same hospital admission) but without ongoing active neurointensive care,, the patient would be eligible but the treating clinician should determine whether it is safe to enrol the patien.

Regarding the post-operative cardiac surgery exclusion criterion - if a patient who had cardiac surgery develops septic shock after PICU discharge, can they be included on readmission to PICU?

The exclusion criterion is for post operative cardiac surgery because treatment protocols are typically prescriptive with regards to blood pressure targets in children immediately post cardiac surgery. However, having had cardiac surgery in the past is not an exclusion criterion (e.g. child with history of VSD repair, presents with septic shock 6 weeks post hospital discharge). In the event of recent surgery (e.g. during the same hospital admission), it will be up to the treating clinician to determine whether it is safe to enrol the patient in the trial.

What is the rationale for inclusion of chronic hypertensive patients, as we would usually aim for a higher MAP in these patients?

There is no proof that permissive hypotension is injurious for chronically hypertensive patients. It is also not feasible to evaluate adequacy of blood pressure control before inclusion in the trial (e.g. at home) in patients identified as chronically hypertensive. Patients classified as normotensive might also have undiagnosed hypertension. This information may not be apparent when we need to make decisions regarding resuscitation targets.

There is a special population on my unit in whom there is not clinical equipoise – can I exclude them from the study?

We do not encourage excluding patients outside the pre-defined exclusion criteria. If you feel there is a specific population in your unit in whom there is not clinical equipoise, please contact the study team to discuss.

Randomisation

What happens if a patient has been re-randomised in error?

Should any errors occur, the expectation is to not re-randomise and let the PRESSURE trial team know as soon as possible so a member of the team can edit the randomisation form for you. If a patient is re-randomised by mistake, you should always follow the first allocation. The second randomisation will be marked by the PRESSURE trial team as an error. You must also document the error in a file note and submit this to pressure@icnarc.org as soon as possible.

Intervention

What if a patient on the permissive arm of the study develops oliguria? Is there scope for increasing the MAP in an attempt to improve urine output?

There is no proof that permissive hypotension is injurious to kidneys even in the face of acute renal failure. Vasoactives induce vasoconstriction and could worsen acute tubular necrosis even if they were, acutely, associated with increased urine output. Various drugs increase urine output without improving renal outcomes (e.g. via efferent > afferent arteriole vasoconstriction, or by modifying tubular reabsorption of electrolytes and water). The only situations where we would ask investigators to discontinue the intervention would be if exclusion criteria arise after randomisation (e.g. brain injury). If MAP is altered in relation to urine output this would be a protocol deviation and an adherence query would be raised.

What if we don't believe that permissive hypotension is safe in chronic hypertension or renal failure?

Despite no evidence to support the claim, even if there is more risk of harm to the kidneys from permissive hypotension, the study rationale is that that the overall benefit may outweigh these risks.

If we learn that a patient randomised to the intervention arm normally has a mean arterial blood pressure lower than the lower limit of the permissive target, should we apply the permissive hypotension protocol even if this would require administering more vasoactives than we normally would?

No. The protocol only applies if vasoactives are being administered. Once vasoactives are discontinued, whatever the reason, we will not scrutinise the MAP values. In the scenario described above, the most logical next step would be to discontinue vasoactives. If vasoactives were still required but the treating team decided that, for whatever reason, the optimal MAP target is below the 5th centile threshold (lower limit of target range), this would not constitute a protocol deviation, in keeping with the overarching aim of the intervention.

How long should the intervention be applied?

The MAP of patients in the intervention arm should be maintained in the target range for as long as they receive vasoactives in the unit. Vasoactives should be discontinued once the patient is able to maintain a MAP value above the 5th centile threshold (lower limit of target range) without vasoactive therapy. In the intervention group, vasoactives should only be restarted if MAP is lower than their allocated target range.

What part of the permissive blood pressure target should we aim for?

Intervention patients should be treated using permissive blood pressure target ranges (lower MAP target 5th centile for age). The aim is to reduce exposure to vasoactive drugs, so weaning down infusion rates/doses of vasoactives should be considered as soon as the patient is above the target MAP range or near to the higher end of the range.

What MAP target should we aim for if the patient is on Usual Care?

Usual care targets should be according to local policy. We accept that different consultants at the same hospital may set slightly different targets. The justification is that PRESSURE is a trial comparing an intervention (permissive MAP target, reduced vasoactive drug exposure) to usual care to determine if the intervention is more beneficial than current practice. If we defined care in the usual care arm (by e.g. increasing the MAP target over and above the usual care MAP target) we would be artificially creating separation between the two groups and the trial's clinical relevance would be limited.

Should the intervention be continued if the patient is readmitted to PICU?

The permissive MAP ranges will apply as long as the patient requires vasoactives whilst on PICU. This includes any readmission from another inpatient area, within 30 days from randomisation. They do not need to be ventilated during this readmission.

The inpatient area can be within your hospital or another hospital they were previously discharged to (it would not be classed as a second admission).

If a patient was discharged home and then readmitted, they would not begin the intervention again.

Do MAP readings need to be invasive i.e. from an arterial line, or can they be from non-invasive?

Either is fine.

Can vasoactives be given peripherally if dose allows?

Yes that is fine.

When should a patient be extubated?

Extubation can happen whenever deemed clinically appropriate. If the patient is still on vasoactives, continue following the intervention target treatment until vasoactives are discontinued.

Should a patient continue on PRESSURE if they are started on ECMO?

If a patient is randomised and then later started on ECMO, it is fine to continue to follow the protocol as long as it is safe to do so.

Consent

A patient was transferred to another PRESSURE participating site shortly after randomisation, who should consent the parents/legal guardians?

If the staff at the randomising site were not able to approach for consent due to timeframes, the new hospital can take over this process and follow the necessary consent procedures. Please ensure communication between sites to determine the progress of this. The new site will continue all treatment data collection according to the protocol from the timepoint of the handover.

What do we do if a patient dies but the parents were not approach for consent prior to this?

Please follow guidance in SOP 005 Consent Procedures. Approach for consent should continue using the bereaved Patient Information Sheet and Consent Form.

Data collection

For patients receiving RRT during their admission should fluid being removed via haemofiltration be included in the "urine output" section of the CRF?

No, only urine being produced by the patient should be included within the "urine output" field of the CRF. This is to allow us to accurately assess patient's kidney function during the study.

Our local system records doses of vasopressin in 'IU/kg/hour', rather than 'U/kg/hour'. Is this the same unit of measurement?

Yes, this is the same unit of measurement. IU refers to 'international units'. The dose should therefore be divided by 60 to convert it to U/kg/min (as required on the CRF).

How do I record daily values?

Daily fluid balance is input (any IV and enteral fluids), minus output. The daily urine output is in the total urine volume (ml), please use your standard unit charting time for 24 hours fluid balance from day 2 onwards.

Do we stop recording organ support daily observations if the patient leaves the PICU?

As information on this CRF is part of the primary outcome (composite of mortality and duration of ventilator support) we ask that data is recorded for the full 30 days following randomisation. This includes:

- If the patient is readmitted to your PICU from another inpatient care area in your hospital or the hospital they were discharged to.
- If the patient was transferred to a PICU not participating in PRESSURE. We ask that you please do your best to contact the hospital to collect the data.

Observations on this page should only be made unobtainable if the patient has died. Please see SOP 007 and 008 for further details.

What happens if a patient is transferred to another hospital site?

If a patient is due to be transferred, we ask you to contact the PRESSURE trial team at ICNARC to let them know. If the patient is transferred to another PRESSURE site, this new site will continue all treatment data collection according to the protocol from the timepoint of

the handover. It is the responsibility of the randomising hospital to complete all data, and consenting processes, up to this timepoint. Once this is complete the patient will be transferred on MACRO and the new site will takeover.

If a patient is transferred to a site not participating in PRESSURE, it is the responsibility of the randomising hospital to complete all data up to this timepoint and consenting processes. We ask for you to contact the non PRESSURE participating hospital to obtain at least the organ support daily observations (the respiratory support details in particular) and the ultimate hospital discharge information following transfer.

When do we start data collection if consent is yet to happen?

Participant data collection can begin immediately and should be recorded on MACRO. If consent is refused or later withdrawn, all data occurring up to the point of this decision will be retained and a minimised anonymised dataset will be collected and retained for monitoring safety and important outcomes in the trial, unless explicitly requested otherwise.

How do I record extubation time for a tracheostomy patient?

Please use the date/time of discharge as the time of 'successful extubation' on the outcomes- at hospital discharge CRF. Please also add a comment to explain this and let us know when the patient came off the ICU ventilator back onto their own NIV ventilator/no support.

Is there a withdrawal form?

No. The Withdrawal of Consent eCRF should only be used if the parents/guardians have explicitly withdrawn consent from aspects they previously consented to. The change to each of these, and a reason for the withdrawal, should be recorded on the eCRF. All data collected up to the point of withdrawal or non-consent will be retained in the trial, unless the parent/legal guardian explicitly requests otherwise.

How do we record PRESSURE patients on EDGE/LMPS?

When you upload site recruitment onto EDGE/LMPS, the PRESSURE team will confirm this number via CPMS each month. The date of consent should be the same as date of randomisation, otherwise it may not be accepted on to your system.

How should PICANet be recorded?

Please use PRESSURE followed by the trial ID, 'PRESSURE-XXXXXX'.

Serious adverse events

Should adverse events and serious adverse events be reported only in the intervention arm?

No. Both the specified and unspecified adverse events, regardless of severity, may be attributable to the lower MAP values in the intervention arm and/or to the anticipated higher doses of vasoactives in the control arm. In fact, it may be impossible to know with certainty what caused the adverse event, in either arm. For example, if a patient who is in shock is treated with high doses of vasoactives to achieve the MAP target, extremity necrosis could

be attributed to either low MAP values or the dose of vasoactive. It is crucial to report adverse events as objectively as possible in both arms of the trial to avoid bias.