PRESSURE Trial

FAQs

Eligibility

*Can patients admitted from theatre with vasoactives already commenced (within prior 6 hours), if they are deemed to have hypotension, be included?*

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 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 vasoactive infusion was started within the last 6 hours and the retrieval team believe the infusion will continue for more than 6 hours; and 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.

*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 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).

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.

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 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 meant to reduce 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 cardiac arrest patients. If the clinical team can rule out this contraindication (e.g. brief cardiac in-hospital arrest for whatever reason, 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 neurological resuscitation interventions, it will be up to the treating clinician to determine whether it is safe to enrol the patient in the trial.
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 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 outwith 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.

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 randomization (e.g. brain injury).

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 will 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.

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).

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.