Appendix
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Supplementary Appendix

S1. List of approved protocol modifications

Version Number	Approval Date	List of Modifications
1 (Original)	06/03/2017	-
1.1	16/07/2017	• Addition of study sites (Children's Hospital Westmead, Sydney; Perth Children's Hospital) • Addition of investigators • Inclusion of planned secondary analyses • Change to randomisation stratification • Inclusion of additional exclusion criteria • Consent form modification • Further detail on instructions on gas flow across all sites, safety cut offs (Met Hb) • Further detail on data collection and blood sampling procedures
1.2	20/11/2017	• Addition of study site (Utrecht Medical Centre, The Netherlands) • Clarification on censoring outcomes at 28 days • Inclusion of additional exclusion criteria • Further detail on consent processes
1.3	18/07/2018	• Addition of neurodevelopment assessment with funding infrastructure • Addition of socioeconomic Survey • Addition of hyperoxia as pre-planned analyses

		• Revision of study sample size
1.4	10/10/2018	• Updating information on Queensland Children's Hospital • Accessing medical records from other healthcare facilities • Blood collection for inflammatory biomarkers optional on consent form

S2. Definition of outcomes

Primary Outcome

The primary outcome of VFD will be calculated as the sum of all episodes of invasive respiratory support, which require an endotracheal tube in situ, from start of CPB and censored at 28 days after CPB start. Patients who die within this time period will be assigned a value of zero for the VFD outcome. Ventilated days do not include non-invasive ventilation or high-flow nasal cannulae. Patients who receive a tracheostomy will be counted as ventilated as long as they receive positive pressure ventilation through the tracheostomy. The individual components of VFDs (duration of invasive respiratory support from start of CPB within the first 28 days, and death within the first 28 days) will also be presented.

Secondary Outcomes

The main secondary outcome is defined by a composite of presence of LCOS, extracorporeal life support (ECLS), or all-cause death.

- The presence of LCOS (1) will be calculated as a binary variable by evaluating the relevant data items at the following time-points: admission to PICU, and after six hours, 12 hours, 24 hours, and 48 hours post-PICU admission, or until the patient is discharged from PICU (whichever occurs first). Criteria for LCOS include a blood lactate level (arterial where available, if not then venous) >4 mmol/L and the presence of an oxygen extraction of greater than 35% (SaO_2-$ScvO_2$ gradient >35%), or a high inotrope requirement operationalised as Vasoactive-Inotrope Score (VIS) ≥15 (2, 3). If these criteria are met for at least one of the above listed timepoints, the presence of LCOS is confirmed. If individual data items required for the calculation of LCOS are missing, then the patient will be assumed not to have had LCOS.

- ECLS post-CPB during the first 48 hours after CPB start.
- Mortality is defined as all-cause death within the first 28 days after CPB start.

Additional secondary outcomes include PICU and hospital length of stay, which will be measured from start time of CPB. In patients discharged alive from the PICU to the ward and readmitted within 72 hours the subsequent PICU admission duration will be added to the index admission. Length of stay (both PICU and hospital) will be censored at 28 days or when the patient was last alive, whichever occurs earlier. Patients who die during their PICU or hospital admission will be assigned the time to event.

Process of care measures will include the use of ECLS (as defined above); duration of time with open chest post-operatively within the first 28 days (as all surgeries will have an open chest during theatre, the time measure will start with admission to PICU, and will include time spent with open chest in cases of emergency secondary reopening); treatment and duration of treatment with inhalational NO from admission to PICU post-operatively within the first 28 days; and treatment and duration of treatment with renal replacement from admission to PICU post-operatively within the first 28 days (defined as the use of peritoneal dialysis or continuous renal replacement therapy [CRRT]). Duration of treatment with inhalational NO post-operatively and duration of treatment with renal replacement post-operatively will be restricted to those patients receiving these treatments.

Organ dysfunction will be assessed at admission to PICU, after 24 hours and after 48 hours, and will be defined by using the cardiovascular, respiratory, renal, neurological, and haematological components of the Paediatric Logistic Organ Dysfunction-2 (PELOD-2) scores (4). If score items are missing then it will be assumed that value was normal for the purpose of the score.

Postoperative Acute Kidney Injury was assessed using serum creatinine levels to classify according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (5). Because no baseline creatinine values were available, we applied the age-specific thresholds used in PELOD-2 to define the presumed baseline creatinine values. KDIGO Stage 1 was defined as an increase in creatinine to 1.5 to 1.9 times the presumed baseline; Stage 2 as an increase 2.0 to 2.9 times; and KDIGO 3 as an increase ≥3.0 baseline and/or the use of RRT.

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List of planned figures

- Figure 1. CONSORT participant flow diagram
- Figure 2. Cumulative incidence functions for extubation (accounting for mortality) (all patients, and the pre-specified subgroups)
- Figure 3. Composite figure of a) bar chart depicting proportion of patients with LCOS, b) mean (and 95% CI) SaO_2-$ScvO_2$ difference, c) boxplot of lactate levels, d) boxplot of VIS score, e) mean (and 95% CI) of creatinine values, over time points 0, 6, 12, 24, 48 hours after PICU admission, f) PELOD-2 score at 0, 24, 48 hours after PICU admission, separated by treatment group

List of planned supplementary material

- Funding sources
- Trial committee and NITRIC trial investigators
- Data and Safety Monitoring Board Terms of Reference
- Data and Auditing Monitoring Plan
- Enrolment statistics by site and country
- List of congenital heart disease conditions and surgeries
- List of protocol violations
- Results of interim analyses
- Consent details
- Volume of blood product transfused between study arms
- Listing of adverse events
- Kaplan-Meier survival curves for length of PICU stay and length of hospital stay
- Results of subgroup analyses
- Forest plot of the treatment effect across subgroups for the primary and secondary outcomes.
- Results of sensitivity analyses

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