A Randomised Multiple Centre Trial of Conservative versus Liberal Oxygenation Targets in Critically Ill Children

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Version history

Version	Date	Summary of main changes/justification	Timing
1.0	03 November 2021		
1.1	02 August 2022	Change to timing of analysis to allow for early reporting of short term outcomes after completion of 30 day follow-up for all patients. Simplified treatment of missing organ support data, based on locations of care	After recruitment ended but before database lock and before inspection of any endpoints.
1.2	02 November 2022	Classification of economic outcomes into primary and secondary, for consistency with protocol. Corrected detail of how heart rate should be adjusted for age, for subgroup analysis.	After recruitment ended but before database lock and before inspection of any endpoints

Contents

1 Introduction

1.1 Background and rationale

The administration of oxygen is a fundamental part of care in paediatric critical illness with supplemental oxygen offered to nearly every acutely unwell child. However, the optimal targets for systemic oxygenation are unknown. Observational data suggest harm from too generous use of supplemental oxygen in adults and children. However currently, there is no high-quality evidence from randomised controlled trial (RCT) data to support this practice and guide clinicians' use of oxygen. Therefore the OXY-PICU trial has been designed to determine whether a conservative target of peripheral oxygen saturation of 88-92% has better clinical outcomes than a more liberal target of >94%.

This document describes the proposed Statistical Analyses Plan (SAP) for the trial. The SAP is agreed in advance of inspecting the outcome data for the trial, so that data-derived decisions in the analyses are avoided. This SAP has been prepared in accordance with published guidelines[1].

1.2 Aim and Objectives

The overall aim of Oxy-PICU is to determine if the risks of interventions employed on intensive care to raise peripheral oxygen saturation to >94% exceed their benefits when compared to a peripheral oxygen saturation of 88-92%.

1.2.1 Primary Objectives

- Composite outcome of mortality and duration of organ support at 30 days (rank-based analysis with death ranked as worse than 30 days of organ support)
- Incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 12 months

1.2.2 Secondary Objectives

- Incremental costs at 30 days
- Mortality at PICU discharge, 30 days, 90 days and 12 months
- Time to liberation from ventilation
- Duration of organ support
- Length of PICU and hospital stay
- Functional status at PICU discharge
- Health-related quality of life (HrQoL) at 12 months

2 Study Methods

2.1 Trial design

Oxy-PICU is a pragmatic, open, multiple centre parallel group randomised controlled trial with integrated economic evaluation in infants and children accepted for unplanned admission to a participating PICU.

2.2 Randomisation

Patients will be randomised on a 1:1 basis to either a liberal (>94%) or conservative (88-92%) SpO2 target, using minimisation to balance the arms with respect to age (<12 months / ≥12 months); site; primary reason for admission (lower respiratory tract infection vs. Other); and severity of abnormality of gas exchange: SF ratio <221 with PEEP ≥5 vs. Other.

2.3 Sample size

The primary clinical outcome will be analysed using rank-based methods, with death at 30 days ranked as the worst outcome. To achieve 90% power, using simulations based on data from the Oxy-PICU pilot RCT, to detect a clinically meaningful reduction in the mean duration of organ support of 12 hours from 120 to 108 hours and assuming no impact on 7.5% mortality requires a total sample size of 2040 patients (allowing for withdrawal/refusal of deferred consent of 10%).

2.4 Framework

The primary clinical outcome, and specified secondary outcomes will be tested for superiority.

2.5 Analysis of internal pilot

The internal pilot phase was evaluated 6 months after the first site has opened to recruitment. At this point the following key progression criteria were assessed and classified as green, amber or red:

	Green	Amber	Red
Number of sites open to recruitment	≥10	6-9	<6
Recruitment rate (per site per month)	≥4.5 (≥75% of anticipated)	3-4.5 (40-75% of anticipated)	<3 (<40% of anticipated)
Separation in mean measurements between groups	SpO_2: ≥3% OR FiO_2 concentration: ≥0.1	SpO_2: 1.5-3% OR FiO_2 concentration: 0.05 – 0.09	SpO_2: <1.5% OR FiO_2 concentration: <0.05
Treatment adherence – carried out per protocol	≥75% cases	50-75% cases	<50% cases

Mean measurements of SpO2 and FiO2 were calculated using all available post-randomisation recorded values for all randomised patients while remaining on invasive ventilation.

Treatment adherence was calculated as the percentage of patients classified as adherent, divided by the total number of randomised patients. A patient was defined as adherent if no potential deviations have been recorded in the first seven days of treatment, where a deviation is classified as either of the following:

- at least four consecutive hourly measurements (constituting three consecutive hours) where the SpO2 is below the target range and both the FiO2 and MAP has stayed constant (or decreased) over all four observations.
- at least four consecutive hourly measurements (constituting three consecutive hours) where the SpO2 is above the target range and the FiO2 and/or MAP (if >16) has stayed constant (or increased) over all four observations.

2.6 Statistical interim analysis and stopping criteria

A single interim analysis will be carried out, after recruitment and follow-up to day 30 of the first 1020 patients. At this point, the primary clinical endpoint will be compared between arms, with early termination of the trial recommended if either arm is shown to be superior with $p<0.001$ (Peto-Haybittle stopping rule).

2.7 Timing of final analysis

The trial database will be locked and the main analysis of the trial will be performed after all patients randomised to the trial have reached their 30 day follow-up timepoint, with one further update of long term outcomes only planned once all patients have reached their 12 month follow-up timepoint.

2.8 Timing of outcome assessments

Following randomisation, observations are recorded hourly on the hour (+/-15 minutes) for 7 days (or until PICU discharge if earlier) and include receipt of invasive ventilation (yes/no) and, where children are on invasive ventilation, SpO2, mean airway pressure (MAP), and FiO2. For days 8 onwards (or until PICU discharge if earlier), the same observations are recorded twice daily at 09:00 and 21:00 (+/- 1 hour).

Receipt of any other type of organ support (yes/no) is recorded once daily until day 30 or PICU discharge.

Other outcomes are collected at discharge from critical care (date/time of liberation from ventilation, survival status at PICU discharge and discharge method, and functional status as measured using the Paediatric Cerebral Performance Category (PCPC) and Paediatric Overall

performance Category (POPC)), and at ultimate discharge from acute hospital (survival status at hospital and ultimate PICU discharge, locations of care after PICU discharge).

Specified adverse events and serious adverse events are collected from randomisation until 30 days after randomisation or discharge from PICU, whichever is later.

Long term survival is collected at 12 months, using either linkage to national survival data (NHS Digital) or by local research teams. Once 12 month survival status is known, PEDS-QL and CHU-9D quality of life questionnaire will be emailed or posted to consenting parents/legal guardians.

3 Statistical Principles

3.1 Confidence intervals and p-values

The primary clinical outcome will be tested for superiority. Other secondary outcomes will be tested for superiority, where testing is specified, or summarised and reported using descriptive statistics. Statistical tests will be two-sided with significance set at $P<0.05$ unless otherwise specified. Effect estimates will be reported with 95% confidence intervals. There will be no adjustment for multiple testing. The results of subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects[2,3].

3.2 Adherence and protocol deviations

3.2.1 Exposure

Exposure to the intervention will be assessed by the following parameters, which will be calculated for each treatment group and summarised using descriptive statistics (mean, standard deviation, median and interquartile range (IQR), or counts and percentages for binary and categorical variables) unless otherwise specified:

- SpO2 recorded while on invasive ventilation
- SpO2 recorded while on invasive ventilation with supplemental oxygen (FiO2 >0.21)
- FiO2 recorded while on invasive ventilation
- Hours of invasive ventilation within the following categories: SpO2 >92% with FiO2=0.21; SpO2 >92% with FiO2 >0.21; SpO2 88-92%; SpO2 <88%, both overall and as a percentage of total hours of ventilation.

Further treatment patterns across each group will be explored using summary statistics and graphic methods only, no formal statistical testing will be performed.

3.2.2 Protocol adherence

The number and % of patients with at least one potential protocol deviation (as defined previously in section 2.5) will be reported, and the total number of such deviations.

3.3 Analysis Population

Following the intention to treat (ITT) principle, all randomised patients will be included in the analysis of the primary clinical endpoint, excluding only those where consent to access medical records was withheld or unobtainable (or were lost to follow-up before PICU discharge for any other reasons) before 30 days post randomisation.

A sensitivity analysis will be conducted in the per-protocol (PP) population, consisting of all randomised patients excluding those who were found to have breached the eligibility criteria following randomisation, and those where a clinical decision not to follow the trial treatment was recorded immediately post randomisation.

4 Trial population

4.1 Screening data

Screening logs will be used to record all patients who are admitted or accepted for admittance to critical care. The following summary measures will be reported:

- Number and % of patients who did not meet inclusion criteria, overall and by criteria
- Of the patients who met the inclusion criteria, number and % who met exclusion criteria, overall and by criteria.
- Of the eligible patients (i.e. met inclusion criteria and did not meet exclusion criteria), number and % not randomised, overall and by reason (if known)

4.2 Eligibility

4.2.1 Inclusion Criteria

- Less than 16 years and more than 38 weeks corrected gestational age
- Enrolled within six hours of first meeting all the following criteria;
  - Accepted to a participating PICU as an unplanned admission
  - Receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange
  - Face-to-face contact with PICU staff or transport team

4.2.2 Exclusion Criteria

- Not expected to survive to ICU admission
- Brain pathology/injury as primary reason for admission (e.g. traumatic brain injury, post-cardiac arrest, stroke, convulsive status epilepticus without aspiration)
- Known pulmonary hypertension
- Known or suspected sickle cell disease
- Known or suspected uncorrected congenital cardiac disease
- End-of-life care plan in place with limitation of resuscitation
- Receiving long-term invasive mechanical ventilation prior to this admission
- Recruited to Oxy-PICU in a previous admission

4.3 Recruitment

A CONSORT flow diagram will be completed to describe number of patients randomised and availability of primary clinical endpoint and 12 month follow-up data within each arm.

4.4 Consent

The parent/legal guardian of trial participants will be asked to consent to the study as soon appropriate and practical after randomisation (usually within 24-48 hrs of randomisation but the timing will vary according to the child's clinical situation). They may consent to any one or more of the following aspects: Trial continuation (i.e. treatment); access to medical records for ongoing data collection; completion of the parental stress questionnaire (at/around the time of consent); to receive a follow-up questionnaire at 6 months post-randomisation; sharing of anonymised data to support future research; to be contacted regarding future research participation. When consent is refused for access to medical records (regardless of whether or not consent has been given for trial continuation), all trial data collection should cease and no data linkage to PICANET or NHSDigital should be performed. Data collected by site staff directly to the trial CRF up to the point of consent refusal will be retained and used for analysis, but no events after this point will be recorded or reported on. If any data has already been obtained via linkage from PICANET or NHSDigital, this data will be deleted.

Where consent has been refused for trial continuation, but granted for access to medical records, data collection and linkage may continue and the patient may be included in the analysis as appropriate for each endpoint.

If consent is refused for access to medical records and/or trial continuation, the parental stress questionnaire may still be completed and reported on if this has been consented to.

4.5 Withdrawal/follow-up

Once given, consent can be withdrawn at any time up to the end of the study. Data collected up to the point of non-consent or withdrawal of consent to data collection will be retained.

4.6 Baseline patient characteristics

Baseline data is collected at critical care admission via data linkage to PICANET, and directly via trial CRF for physiology at randomisation. The following baseline demographic and clinical data will be summarised in the ITT population, by allocated treatment group, (using mean, standard deviation,

median and interquartile range (IQR), or counts and percentages for binary and categorical variables), but not subjected to statistical testing:

Age (years)– median and IQR, and number and % by age group (<=12 months, >12 months))

Ethnic group

Sex (male, female) – number and %

Arterial PaO2, base excess, lactate, systolic blood pressure, and mean airway pressure at randomisation – median and IQR, mean and SD

Comorbidities – number and % by type of comorbidities (as specified on the CRF)

Main reason for PICU admission (from PICANET linkage)

5 Analysis

5.1 Outcome definitions

5.1.1 Primary clinical outcome

The primary clinical outcome is a composite of death and organ support by 30 days. Patients who have died on or before day 30 post randomisation are assigned the worst possible score of 31, and surviving patients are scored by the number of calendar days on which any type of organ support was given, starting from day 1 (the day on which the patient was randomised) up to and including day 30. Any organ support during the first 30 days will be included, regardless of whether the support was during the index PICU admission, on a ward, or during a re-admission to PICU.

5.1.2 Primary health economic outcomes - Incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 12 months

Economic costs will be calculated from patient-level resource use data captured through trial case report forms linked to PICANet, Hospital Episode Statistics, and follow-up patient questionnaire. Resource use for delivering the interventions, length of stay in PICU/HDU and acute hospital, for the index admission and any readmission before 12 months, and from use of personal health services after acute hospital discharge within 12 months post-randomisation will be measured. Appropriate unit costs data will be obtained from the NHS Payment by Results database, unit costs of health and social care (PSSRU) and from local Trust Finance Departments.

The health outcome for the economic evaluation will be summarised using QALYs, which unites quantity (survival) and quality of life into a single metric. To do this, HRQoL, which is measured on an index scale of 1 (equals full health) and 0 (equals death), at 12 months will be assessed using the Paediatric Quality of Life Generic Core Scales (PedsQL) and CHU-9D instruments. HRQoL data will be collected via age-appropriate Paediatric Quality of Life Generic Core Scales (PedsQL) and Child Health Utility 9D (CHU-9D) questionnaires sent to surviving children at 12 months. The responses to PedsQL questionnaire from eligible surviving children at 12 months will be mapped onto the Child Health Utility 9D (CHU-9D) score (Lambe et al, 2018). The responses to CHU-9D questionnaire will be converted into utility score using recommended algorithm (Stevens, 2012). QALYs will be calculated by valuing each patient's survival time by their HRQoL at 12 months according to the "area under the curve" approach. For 12-month survivors, QALYs will be calculated using the HRQoL scores at 12 months, assuming HRQoL of zero at randomisation, and a linear interpolation between randomisation and 12 months. For decedents between randomisation and 12 months, we will assume zero QALYs.

5.1.3 Secondary outcomes

5.1.3.1 Incremental costs at 30 days

Costs at 30 days will be calculated from patient-level resource use data, length of stay in PICU/HDU and acute hospital, for the index admission and any readmission before 30 days.

5.1.3.2 Mortality at PICU discharge, 30 days, 90 days and 12 months

Mortality at discharge from the critical care unit will be defined as death due to any cause before discharge to any location providing a level of care less than Level 2 (high dependency care).

5.1.3.3 Time to liberation from ventilation

Liberation from ventilation is defined as the start of a continuous period of at least 48 hours free from ventilation. The time to liberation from ventilation will be measured from randomisation to the start of the first such period.

5.1.3.4 Duration of organ support.

Duration of organ support is defined as for the primary clinical endpoint (number of calendar days from day 1 to 30 on which any support was given).

5.1.3.5 Length of PICU and acute hospital stay

Length of PICU stay will be measured in hours from randomisation to discharge, plus the duration from admission to discharge of any subsequent re-admissions to a PICU starting up to and including day 30.

5.1.3.6 Functional status at PICU discharge

Functional status at PICU discharge will be measured in surviving patients at the time of first discharge from PICU following randomisation, using the Paediatric Cerebral Performance Category (PCPC) and Paediatric Overall Performance Category (POPC) scales, which categorise performance on a 5 point scale from best (1) to worst (5).

5.1.3.7 Health related quality of life at 12 months

Health-related quality of life at 12 months will be measured using the Paediatric Quality of Life Inventory (Peds-QL)32 and the Child Health Utility 9D (CHU-9D), completed by parents at twelve months post-randomisation.

The PEDS-QL instrument uses a different set of question of each age group of 1-12 months; 13-24 months; 2-4 years; 5-7 years; 8-12 years; 13+years. For each age group an overall score is calculated on a scale of 0-100 with higher scores indicating better quality of life. In infants under 2 years five subscales are defined, relating to physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning, and in children of 2 years and over four subscales are defined, relating to physical functioning, emotional functioning, social functioning and school functioning.

CHU-9D was developed with children aged 7-17 and is designed to produce utility values for use in calculating quality adjusted life years (QALYs)

5.2 Clinical effectiveness analysis methods

5.2.1 Primary outcome

The primary clinical outcome will be compared between arms using a Wilcoxon rank-sum test with two-sided p-value of 0.05. 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 organ support), which will be presented with a 95% confidence interval.

Ordered logistic regression will be used firstly in a sensitivity analysis to estimate the unadjusted proportional odds ratio, and secondly to estimate the proportional odds after adjusting for the following baseline variables:

- age (<12 months / ≥12 months);
- primary reason for admission (lower respiratory tract infection vs. Other);
- severity of abnormality of gas exchange: SF ratio <221 with PEEP ≥5 vs. Other
- predicted mortality at PICU admission (measured using the PIMS 3[4] score)
- site (as a random effect)

Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the following baseline covariates:

- age (<12 months / ≥12 months);
- Age adjusted heart rate centile
- Haemoglobin level at admission

The interaction effect for continuous covariates (haemoglobin at admission) will be illustrated by calculating the adjusted hazard ratio within five categories at quintiles of the continuous variable. Heart rate will be corrected for age by grouping into centile bands[5].

5.2.2 Secondary outcomes

Mortality at discharge from critical care and at 30 days will be compared between groups using Fisher's exact test. If the number of events allows, logistic regression will be used to compare mortality between groups adjusted for baseline variables.

Mortality at 90 days and at 12 months will be estimated by arm, using Kaplan-Meier methods with patients censored at last available follow-up. If the number of events allows, Cox regression will be used to compare mortality between groups adjusted for baseline variables.

Time to liberation from ventilation will be reported as median time (with 95% confidence interval) by arm, calculated using Kaplan-Meier methods. Unadjusted and adjusted hazard ratios will be calculated using Cox regression. Patients who die on ventilation will be censored at date & time of death.

Duration of organ support to day 30 (calculated as for the primary clinical endpoint) will be compared between groups using a Wilcoxon rank-sum test, in patients stratified by survival status. Duration of organ support by type of support (respiratory invasive; respiratory non-invasive; cardiovascular; renal; other) will be reported by group using medians and interquartile ranges, and counts and percentages of patients ever receiving, but not formally tested for differences between groups.

Length of PICU and acute hospital stay will be compared between groups using a Wilcoxon rank-sum test, and reported by group using medians and interquartile ranges, in patients stratified by survival status.

Functional status at PICU discharge will be reported as counts and percentages in each of five possible categories.

All adjusted analysis will include the baseline variables previously listed in section 5.2.1.

5.2.3 Sensitivity analyses

Analysis of the primary clinical endpoint, and relevant secondary endpoints, will be repeated with duration of organ support measured in calendar days from randomisation to the last recorded day of organ support (capped at day 30). Duration of respiratory support will be reported using Kaplan-Meier methods with time measured from randomisation to the end of the last known period of respiratory support which started on or before day 30.

Unadjusted treatment effects for the two components of the composite primary clinical endpoint (days or organ support, and mortality by day 30) will be compared to confirmed that any treatment effect is in the same direction for both components. If this appears not to be the case, the partial proportional odds model[6] will be used to estimate adjusted treatment effects.

5.3 Cost effectiveness analysis methods

A full cost-effectiveness analysis (CEA) will be undertaken to assess the incremental cost and net monetary benefit of the intervention, according to the intention-to-treat principle. Resource use and outcome data collected as a part of the OXY-PICU trial will be used to report cost-effectiveness at 12 months by randomised treatment group.

The cost analysis will take a health and personal health services perspective. The primary sources of the resource use data will be the OXY-PICU trial case report forms (CRFs), PICANET data, hospital episode statistics (HES) database and health service questionnaires (HSQ) on the use of personal health services which are posted to parents/guardians of surviving patients at 12 months following randomisation. Resource use data from the PICU/HDU stay will be taken from the CRF and linked to routine data from PICANet. Data on the level of care for PICU/HDU bed-days will be gathered through routine collection of the Paediatric Critical Care Minimum Dataset (PCCMDS) in the participating centres via the PICANet database. Information on subsequent PICU/HDU and hospital admissions will be obtained via data linkage with PICANet and HES database. Use of primary care and community health services will be assessed by HSQ at 12 months. Resource use data from the trial datasets, PICANet data, HES database and 12 months follow-up questionnaires will be combined with appropriate unit costs to report the total costs per patient at 12 months for both randomised groups.

Missing data in costs and HRQoL will be handled with multiple imputation, assuming the data are missing at random (MAR) conditional on the observed data (see below for details on methods used to handle missing data). On the imputed datasets the cost-effectiveness analysis will use a Bivariate Seemingly Unrelated Regression model to allow for correlation between costs and QALYs and multilevel structure of the data. We will calculate the interclass correlation coefficient (ICC) which measures the proportion of the overall variation that occurs at the cluster level . If ICC>10% we will

use multilevel models (MLM) to handle clustering and avoid potential biases and incorrect inferences. The CEA will adjust for same baseline covariates as for the analysis of primary clinical outcome to adjust for baseline imbalances between the randomised arms The incremental results from multiply-imputed datasets will summarised using Rubin's rule {Rubin, 1987 #54}.

The CEA will report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 12 months. Incremental costs at 30 days will also be reported. The incremental net monetary benefit (INB) of the intervention compared to control at 12 months will be calculated by multiplying the mean gain or loss in QALYs by a recommended thresholds in the UK (£20,000) and subtracting the incremental cost. The probability that the intervention is cost-effective compared to control will be presented at different levels of WTP for a QALY gain.

5.3.1 Sensitivity analysis for cost-effectiveness

The following sensitivity analyses will be performed to check the robustness of primary CEA results at 12 months.

a. HRQoL data

Alternative mapping algorithms for converting PedsQL responses to CHU-9D scores will be explored(Lambe et al., 2018). We will also explore alternative distributional assumptions for QALYs.

b. Cost data

Because of the likely skewed distribution of costs, we will consider several distributions that can give a better fit of cost data. We will assess the implications of potential double-counting of inpatient costs across the three sources of resource data.

5.4 Handling of missing data

The amount of missing data for the survival component of the primary clinical outcome is assumed to be minimal. Patients who consent to data collection and were subsequently lost to follow-up after discharge from PICU but before 30 days are assumed to be alive at day 30 with no subsequent PICU readmissions. All patients discharged from hospital before day 30 are assumed to have survived to day 30.

Where a single day of organ support data is missing, but the patient has known to have received organ support on the previous and next day, we will assume that organ support was also received on the missing day. We will also assume that no organ support was given on the day of hospital discharge, unless otherwise recorded.

For the interim analysis, a complete case analysis will be presented (including only patients with complete data for the primary clinical endpoint, after making the above assumptions), and additional sensitivity analyses will be performed showing results under three different possible scenarios: i) on days where organ support data is missing, at least one form of support was provided if the child was known to be in a PICU, and not given otherwise (regardless of treatment allocation), ii) organ support is provided on all missing days for patients in the conservative arm and not provided for all missing days for patients in the liberal arm, and iii) organ support is not provided on all missing days for patients in the conservative arm and is provided for all missing days for patients in the liberal arm.

For the final primary clinical analysis where organ support data is missing, we will assume that organ support was given if the patient was known to be located in a PICU/HDU or the location was not known, and organ support was not given if the patient was known to be located on a ward (or was

discharged from PICU/HDU to a ward). The validity of these assumptions will be explored by describing patterns of known organ support by location of care.

For the adjusted analysis, missing baseline variables will be imputed using the Multivariate Imputation using Chained Equations (MICE) algorithm, with the model including all baseline variables included in the adjusted models. The number of imputations will be determined according to level of missingness. Models will be fitted in each imputed dataset and results combined using Rubin's rules.

Patients who withdrew or withheld consent from data collection will not be included in the primary clinical endpoint analysis, but will be included in sensitivity analyses, firstly with all patients in the intervention group with missing outcomes assumed to have died by day 30, and all patients in the control group assumed to have survived with no further days of organ support, and secondly with the opposite assumptions, to give the absolute range of how much the results could change if the data were complete.

5.5 Additional analyses

5.6 Safety

Adverse events (severe lactic acidosis, cardiac ischaemia, acute kidney injury, and seizures) and any other possibly related adverse event, are recorded from randomisation until 30 days after randomisation or discharge from PICU, whichever is later

The percentage of patients experiencing one or more adverse event will be compared between groups using Fisher's exact test. Counts and percentages of adverse events, and serious adverse events, overall and by type, will be presented by allocated treatment group. Safety results will be reported for the ITT and PP populations.

5.7 Statistical software

All analyses will be conducted in Stata/SE Version 16.1 64-bit x86-64 (StatCorp LLC, College Station, TX). Some additional cost-effectiveness analysis may be carried out in R if required.

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