A randomised pilot multiple centre trial of conservative versus liberal oxygenation targets in critically ill children (Oxy – PICU Pilot Study)

Statistical Analysis Plan

Version 1.1, 30/08/2017

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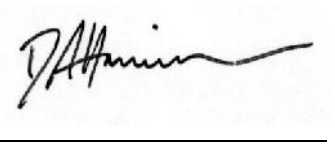
Author:	Dr Jerome Wulff, Statistician

Role, Name and Position	Signature	Date
Chief investigator: Prof. Mark Peters Professor of Paediatric Intensive Care & Hon. Consultant Intensivist, The UCL Great Ormond Street Institute of Child Health		30/08/2017
Senior Statistician: Dr David Harrison Head Statistician, Intensive Care National Audit & Research Centre)		30/08/2017

Version history

Version number	Date	Summary of main changes from previous versions
1.0	23/08/2017	N/A
1.1	30/08/2017	Minor text edits and changes to dummy tables

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Abbreviations

AE	Adverse Event
CATS	Children's Acute Transport Service
CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
GOSH	Great Ormond Street Hospital for Children
ICNARC	Intensive Care National Audit & Research Centre
IQR	Interquartile range
PaO_2	Arterial partial pressure of oxygen
PICU	Paediatric intensive care unit
PIM2r	Paediatric Index of Mortality version 2
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SD	Standard deviation
SGH	Southampton General Hospital
SMH	St Mary's Hospital
SORT	Southampton-Oxford Retrieval Team
SpO_2	Peripherally measured oxygen saturation
UCL	University College London

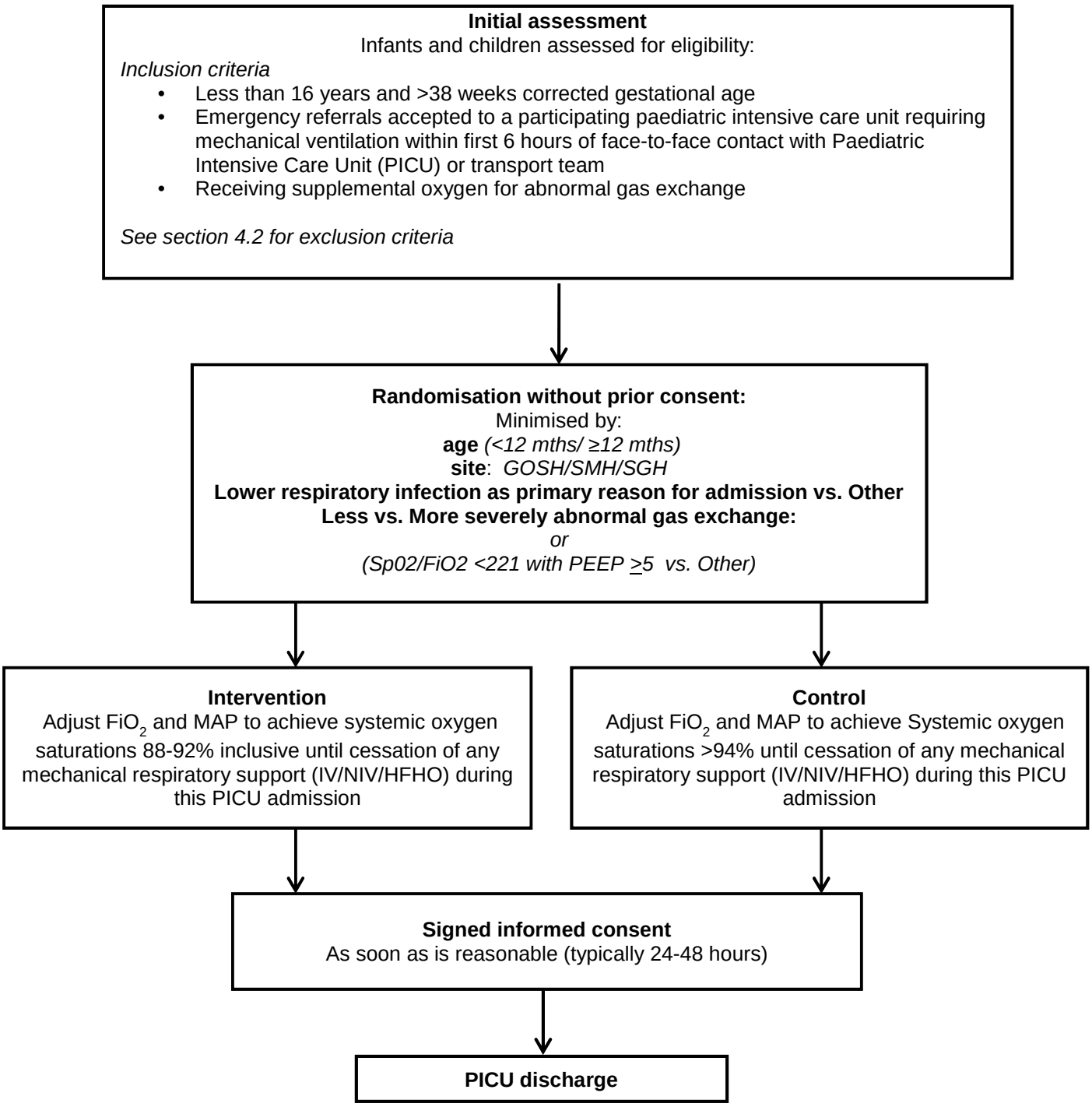
1. Background and rationale

The Oxy-PICU (Oxygenation targets in critically ill children in Paediatric Intensive Care Units feasibility study) trial is a pragmatic, open, pilot randomised controlled trial (RCT) comparing conservative oxygen saturation target (88-92%) with a more liberal target (>94%) to demonstrate feasibility of a definitive large-scale RCT for critically ill children in Paediatric Intensive Care Units (PICUs) in the United Kingdom. The study aims to recruit 120 critically ill children from three NHS hospitals, including associated transport services, over and anticipated six month period. Since these patients will usually require emergency life-saving treatment with supplemental oxygenation, research will be conducted without prior consent and parents/guardians will be approached to discuss participation in the study as soon as is reasonably practical[1-3], usually within 24-48 hours after randomisation. The flow chart of the study is illustrated in Figure 1.

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be carried out to support the completion of the trial manuscripts for publication in the scientific literature and to aid the decision as to whether a definitive trial is feasible. Additional exploratory analyses, including in relation to the samples collected, which may not have been identified in this SAP, may also be performed. Any unplanned analyses not identified in this SAP will be clearly outlined as such in the respective report/manuscript.

This SAP has been agreed in advance of inspecting the outcome data for the Trial, so that data-derived decisions in the analyses are avoided.

Figure 1: Study flow chart



2. Study objectives

2.1 Primary objectives

The primary objective of this study is to determine the feasibility of a large scale RCT (safe, adequately powered, and affordable multicenter) study in critically ill children comparing current practice of liberal targets for systemic oxygen levels with more conservative targets.

The underlying hypothesis of definitive RCT is that the harm of interventions to raise arterial oxygen saturation to >94% exceeds the benefits of these interventions.

2.2 Secondary objectives

The secondary objectives are:

i. To test the willingness of clinicians to screen, recruit and randomise eligible patients

ii. To estimate the recruitment rate

iii. To test, following randomisation, delivery of, and adherence to, the intervention and demonstrate separation between the groups

iv. To test acceptability of the deferred consenting procedures and participant information

v. To test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event (AE) reporting

vi. To inform final selection of a patient-centred primary outcome measure

vii. To estimate the characteristics (e.g. standard deviation) of the selected patient-centred primary outcome measure to inform sample size estimation

viii. To inform content and time needed for final data collection

3. Methods

3.1 Trial design

This study is a pragmatic, open, pilot randomised controlled trial in infants and children accepted for emergency admission to a participating PICU

3.2 Setting

Three PICUs representing typical configurations for UK PICUs (general or combined ICUs in general academic medical centres or within stand-alone children's hospitals).

The study sites are:

- Great Ormond Street Hospital for Children
  - Transport Team: Children's Acute Transport Service (CATS)
- St Mary's Hospital
  - Transport Team: Children's Acute Transport Service (CATS)
- Southampton General Hospital
  - Transport Team: Southampton-Oxford Retrieval Team (SORT)

4. Inclusion and exclusion criteria

The inclusion and exclusion criteria of this study are as described below.

4.1 Inclusion criteria

The inclusion criteria are defined as:

i. Less than 16 years and more than 38 weeks corrected gestational age
ii. Emergency admission accepted to a PICU requiring mechanical ventilation within first 6 hours of face-to-face contact with PICU staff or transport team
iii. Receiving supplemental oxygen for abnormal gas exchange

4.2 Exclusion criteria

The exclusion criteria are children who:

i. Death perceived as imminent
ii. Brain pathology/injury as primary reason for admission (e.g. traumatic brain injury, post-cardiac arrest, stroke, convulsive status epilepticus without aspiration)
iii. Known pulmonary hypertension
iv. Known or suspected sickle cell disease
v. Known or suspected uncorrected congenital cardiac disease
vi. End-of-life care plan in place with limitation of resuscitation
vii. Recruited to Oxy-PICU in a previous admission

5. Outcomes

5.1 Primary outcomes

The primary outcome of this study is the number of patients recruited per site per month.

5.2 Secondary outcomes

The secondary outcomes of this study are as define below:

i. Proportion of parents/legal representatives refusing deferred consent
ii. Proportion of eligible patients randomised (target 50%)
iii. Distribution of time to randomisation
iv. Proportion of systemic oxygen saturations within the target range in each group
v. Proportion of patients in each arm requiring other treatments influencing tissue oxygen delivery (blood transfusion, inotropic support)
vi. Characteristics and completeness of potential primary endpoints for a definitive study including: length of ventilation, length of PICU stay, PICU mortality, days of organ specific support
vii. Observed AEs
viii. Time taken for data collection and entry

6. Power calculation

This study is set up to test the feasibility of the protocol to recruit eligible patients. Therefore, there is no primary outcome to be compared between the two groups and, hence, a usual power calculation to determine sample size is not appropriate. Instead, the sample size has been determined to be adequate to estimate critical parameters to be tested to a necessary degree of precision.

Based on available data from PICANet, it is anticipated that the participating sites will recruit approximately 4-10 children per month, providing a total of approximately 120 children in 6 months.

Recent research has demonstrated that a standard sample size for a pilot study (approximately 30 patients) will result in an imprecise estimate of the standard deviation of a potential outcome measure which will frequently lead to definitive studies that are either underpowered (if the imprecision of the estimated standard deviation (SD) is not taken into account in the sample size calculation) or inefficient (if it is)[4]. Sim and Lewis recommend a sample size of around 60 patients would usually be sufficient to estimate the SD for a continuous outcome measure; however, they note that estimating the precision of a binary outcome will require a larger sample size, typically requiring between 98 and 260 patients[5]. For example, one potential outcome measure for Oxy-PICU is 30-day all-cause mortality, which is anticipated to be in the region of between 5-8% (estimate from PICANet data). The proposed sample size of 120 patients for Oxy-PICU would enable the mortality to be calculated with a precision of approximately ± 5%.

7. Statistical methods

7.1 General analysis issues

7.1.1 Analysis population

All analyses will be based on the intention to treat (ITT) principle. The patients will be analysed according to the group they were randomised to, irrespective of whether the treatment allocated was received.

7.1.2 Analysis software

Analyses will be performed using Stata/SE Version 14.2 for Windows 64-bit x86-64

8. Statistical analysis

Numbers of patients screened and eligible will be reported by site. Numbers of patients randomised, consented, and withdrawn and amount of time to randomisation will be reported both by site and by treatment group. The information will be summarised as a CONSORT flow diagram. Reasons for exclusion and for withdrawal will be summarised, where reported. Also, the number of patients screened and recruited will be reported per month and by site in a table and as a graph.

Baseline demographic and clinical data will be summarised for the ITT population, for each of the two treatment groups and overall. Continuous variables will be summarised as mean (standard deviation (SD)) and median (interquartile range (IQR)) whilst categorical variables will be summarised as number (percent (%)). There will be no statistical testing for any of the summary measures whilst comparing the baseline variables between the treatment groups. The following baseline variables will be compared between the treatment groups and may be required for risk adjustment and stratification:

i. Age;
ii. Gender;
iii. Primary diagnosis for admission;
iv. Any comorbidities;
v. Severity of gas exchange;
vi. Suspected cause of acute respiratory failure;
vii. Weight; and
viii. PIM2r score

For full details of included variables see Appendix.

Organ support (cardiovascular, renal, sedative and others) on the day of randomisation will be reported as number and percentage by treatment group

Interventions received at hour zero (at randomisation) will also be reported as number and percentage or mean (SD) and median (IQR) where appropriate by treatment group

Time spent within the target SpO_2 ranges will be reported between randomisation and hour 24 as:

i. Time SpO_2 in target range (hours) – mean (SD) and median (IQR) by treatment group,
ii. Percentage of time points SpO_2 in target range – mean (SD) and median (IQR) by treatment group

Adherence to the target SpO_2 range will be reported between randomisation and hour 24 as:

Conservative group (target 88-92%)

i. SpO_2 in target range;
ii. SpO_2 outside target range for a single hour;
iii. SpO_2 below target range for two consecutive hours, but with appropriate increase in flow rate, pressure or escalation of type of ventilation, or receiving 100% oxygen; or
iv. SpO_2 above target for two consecutive hours, but with appropriate decrease in flow rate, pressure or de-escalation of type of ventilation.

Liberal group (target >94%)

i. SpO_2 in target range;
ii. SpO_2 below target range for a single hour; or
iii. SpO_2 below target range for two consecutive hours, but with appropriate increase in flow rate, pressure or escalation of type of ventilation, or receiving 100% oxygen.

The number and percentage of patients experiencing each pre-specified adverse event (AE) (plus any other AEs as reported) will be summarised for each treatment group. Numbers of severe adverse events (SAEs), severity and reported relatedness to treatment will be reported in text.

The diagnosis at discharge from PICU will be reported as number and percentage by treatment group.

A comparison by treatment group will be reported for the following outcome measures:

i. Length of PICU stay
ii. Length of invasive ventilation

iii. Length of non-invasive ventilation
iv. Ventilator-free days at day 30
v. Duration of organ support
    a. Days of cardiovascular support
    b. Days of renal support
    c. Days receiving sedatives
vi. PICU mortality

Binary outcomes will be reported as the number and percentage in each group, the risk ratio and absolute risk reduction with 95% confidence intervals. Continuous outcomes will be reported as the mean (SD) and median (IQR) in each group and as the difference in means (95% confidence interval).

Daily organ support will be presented graphically by plotting the percentage of patients in each group receiving each support from day 0 to 15. This will be reported separately for cardiovascular support, renal support and receipt of sedatives.

Ventilator settings and observations will be presented graphically by plotting the mean (SD) of each parameter at the time points recorded (Hourly 0 to 24, then four hourly up to 72 hours. The following will be reported:

- SpO_2 (%)
- SpO_2 in range (%)
- Flow rate (l/kg/min)
- Pressure (cmH_2O) - if CPAP
- Mean airway pressure (cmH_2O)
- FiO_2 (decimal)
- Receipt of invasive ventilation, non-invasive ventilation, high-flow humidified and none (%)

9. Reporting conventions

The following reporting conventions will be used for the SAP. These conventions will enhance the review of the study report and help to standardise presentation with common notations.

i. Sample sizes will be presented for each treatment group as totals in the column header as “(N = xxx)”, where appropriate.

ii. Sample sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.

iii. All summaries for categorical variables will include all categories that were available and will not be restricted to those with at least one response.

iv. Summaries for continuous variables will be reported as n, mean and standard deviation (SD), and median and quartiles.

v. All percentages will be rounded and reported to a single decimal place (xx.x%). A percentage of 0% will be reported as “0%”; a percentage of 100% will be reported as “100%”.

vi. Summaries that include P-values will report the P-value to three decimal places with a leading zero (0.xxx). P-values of less than 0.0005 will be reported as “<0.001” not “0.000”.

vii. Missing values for both numeric and string variables will be presented as dashes (“---”) or as “Not available” / “Not applicable” / “Not reported” (as appropriate) in tables or data listings.

10. Reference

1. Woolfall K, Frith L, Dawson A, Gamble C, Lyttle MD, Young B. Fifteen-minute consultation: an evidence-based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials. Arch Dis Child Educ Pract Ed. 2016;101(1):49-53.

2. Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. BMJ Open. 2015;5(9):e008522.

3. Woolfall K, Young B, Frith L, Appleton R, Iyer A, Messahel S, et al. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. BMJ Open. 2014;4(5):e005045.

4. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004;10(2):307-12.

5. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol. 2012;65(3):301-8.

11. Appendix – proposed tables and figures

Table 1a: Number of patients screened, eligible, randomised, consented, withdrawn, and analysed, and amount of time to randomisation by site

Variables	Site A	Site B	Site C	Total
Number screened, N				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Number of eligible patients, n (% of screened)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Number of patients randomised, n (% of eligible)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Consent obtained, n (% of randomised)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Refused consent, n (% of randomised)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Withdrawal, n (% of consented)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Number of patients analysed, n (% of randomised)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Number of patients analysed but not started treatment, n (% of randomised)				
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XXX
Time to randomisation from first contact				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)

n: Number of patients; %: Percentage; N: Total number of patients

Table 1b: Number of patients randomised, consented, withdrawn and analysed, and amount of time to randomisation, by treatment group

Variables	Conservative	Liberal	Total
Number of patients randomised, n (% of eligible)			
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Consent obtained, n (% of randomised)			
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Refused consent, n (% of randomised)			
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Withdrawal, n (% of consented)			
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Number of patients analysed, n (% of randomised)			
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Number of patients analysed but not started treatment, n (% of randomised)			
n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Time to randomisation from first contact			
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX.X (XX.X)

n: Number of patients

Table 1c: Number of patients screened and recruited per month and by site

Months	Site A	Site A	Site B	Site B	Site C	Site C
	Patients screened	Patients recruited	Patients screened	Patients recruited	Patients screened	Patients recruited
MMM-YY	XX	XX	XX	XX	XX	XX
MMM-YY	XX	XX	XX	XX	XX	XX
MMM-YY	XX	XX	XX	XX	XX	XX
MMM-YY	XX	XX	XX	XX	XX	XX
MMM-YY	XX	XX	XX	XX	XX	XX
MMM-YY	XX	XX	XX	XX	XX	XX

Table 2a: Baseline demographic and clinical variables by treatment group

Variables	Conservative	Liberal	Total
	N = XX	N = XX	N = XXX
Age (years)			
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Age group, n (%)			
< 1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)
1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)
2 to 4 years	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 to 9 years	XX (XX.X)	XX (XX.X)	XX (XX.X)
10 to 16 years	XX (XX.X)	XX (XX.X)	XX (XX.X)
Gender, n (%)			
Female	XX (XX.X)	XX (XX.X)	XX (XX.X)
Male	XX (XX.X)	XX (XX.X)	XX (XX.X)
Weight (kg)			
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Estimated:			
Yes	XX (XX.X)	XX (XX.X)	XX (XX.X)
No	XX (XX.X)	XX (XX.X)	XX (XX.X)
Comorbidities, n (%)			
Cardiac arrest before PICU admission	XX (XX.X)	XX (XX.X)	XX (XX.X)
Cardiac arrest out of hospital	XX (XX.X)	XX (XX.X)	XX (XX.X)
Cardiomyopathy or myocarditis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Severe combined immune deficiency	XX (XX.X)	XX (XX.X)	XX (XX.X)
Hypoplastic left heart syndrome	XX (XX.X)	XX (XX.X)	XX (XX.X)
Leukaemia or lymphoma after first induction	XX (XX.X)	XX (XX.X)	XX (XX.X)
Acute Necrotising Enterocolitis (NEC)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Acute or chronic liver failure	XX (XX.X)	XX (XX.X)	XX (XX.X)
Spontaneous cerebral haemorrhage	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neurodegenerative disorder	XX (XX.X)	XX (XX.X)	XX (XX.X)
Human Immunodeficiency Virus (HIV)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Bone marrow transplant recipient	XX (XX.X)	XX (XX.X)	XX (XX.X)
PIM2r score			
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Acute diagnosis, n (%)			
Severe sepsis / septic shock	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other infection	XX (XX.X)	XX (XX.X)	XX (XX.X)
Congenital heart disease	XX (XX.X)	XX (XX.X)	XX (XX.X)
Arrythmia	XX (XX.X)	XX (XX.X)	XX (XX.X)
Myocarditis / DCM	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other cardiac	XX (XX.X)	XX (XX.X)	XX (XX.X)
OSA	XX (XX.X)	XX (XX.X)	XX (XX.X)
DKA	XX (XX.X)	XX (XX.X)	XX (XX.X)
Inborn error	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other metabolic	XX (XX.X)	XX (XX.X)	XX (XX.X)
Leukaemia / lymphoma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Solid tumour	XX (XX.X)	XX (XX.X)	XX (XX.X)
Acute kidney injury	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other respiratory	XX (XX.X)	XX (XX.X)	XX (XX.X)
Multiple trauma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other trauma	XX (XX.X)	XX (XX.X)	XX (XX.X)

Submersion	XX (XX.X)	XX (XX.X)	XX (XX.X)
Surgical - acute abdomen	XX (XX.X)	XX (XX.X)	XX (XX.X)
Complex or multiple congenital abnormalities	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neuromuscular disease	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asthma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Aspiration pneumonia	XX (XX.X)	XX (XX.X)	XX (XX.X)
Pneumonia / LRTI	XX (XX.X)	XX (XX.X)	XX (XX.X)
Bronchiolitis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Croup	XX (XX.X)	XX (XX.X)	XX (XX.X)
Tracheitis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 2b: Baseline physiology variables by treatment group

	Conservative	Liberal	Total
Variables	**N = XX**	**N = XX**	**N = XXX**
Arterial PaO_2 (kPa):			
Mean (SD)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XXX)	XX (XX, XXX)	XX (XX, XXX)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)
FiO_2:			
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Median (IQR)	X.XX (X.X, X.X)	X.X (X.X, X.X)	X.XX (X.X, X.X)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)
Base excess (mmol l^{-1}):			
Mean (SD)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XXX)	XX (XX, XXX)	XX (XX, XXX)
Arterial	XX (XX.X)	XX (XX.X)	XX (XX.X)
Capillary	XX (XX.X)	XX (XX.X)	XX (XX.X)
Venous	XX (XX.X)	XX (XX.X)	XX (XX.X)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lactate (mmol l^{-1})			
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Median (IQR)	X.XX (X.X, X.X)	X.X (X.X, X.X)	X.XX (X.X, X.X)
Arterial	XX (XX.X)	XX (XX.X)	XX (XX.X)
Capillary	XX (XX.X)	XX (XX.X)	XX (XX.X)
Venous	XX (XX.X)	XX (XX.X)	XX (XX.X)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)
SpO_2 (%):			
Mean (SD)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XXX)	XX (XX, XXX)	XX (XX, XXX)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)
SBP (mmHg):			
Mean (SD)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XXX)	XX (XX, XXX)	XX (XX, XXX)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mean Airway Pressure:			
Mean (SD)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XXX)	XX (XX, XXX)	XX (XX, XXX)
Not recorded	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 2c: Organ support at randomisation by treatment group

Variables	Conservative N = XX	Liberal N = XX
Cardiovascular: n (%)		
Continuous infusion of inotrope	XX (XX.X)	XX (XX.X)
Continuous infusion of vasodilator	XX (XX.X)	XX (XX.X)
Extracorporeal membrane oxygenation	XX (XX.X)	XX (XX.X)
Renal: n (%)		
Peritoneal dialysis	XX (XX.X)	XX (XX.X)
Haemofiltration	XX (XX.X)	XX (XX.X)
Haemodialysis	XX (XX.X)	XX (XX.X)
Plasma filtration	XX (XX.X)	XX (XX.X)
Plasma exchange	XX (XX.X)	XX (XX.X)
Other:		
Sedatives/neuromuscular blockade	XX (XX.X)	XX (XX.X)
Blood transfusion	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;

Table 2d: Interventions at randomisation by treatment group

Variables	Conservative	Liberal
Interventions: n(%)		
Invasive ventilation	XX (XX.X)	XX (XX.X)
Non-invasive ventilation	XX (XX.X)	XX (XX.X)
High-flow humidified oxygen	XX (XX.X)	XX (XX.X)
None received	XX (XX.X)	XX (XX.X)
Ventilator settings:		
Flow rate (l/kg/min):		
Mean (SD)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XX)	XX (XX, XX)
Pressure (cmH_2O) - if CPAP:		
Mean (SD)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XX)	XX (XX, XX)
Mean airway pressure (cmH_2O):		
Mean (SD)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX, XX)	XX (XX, XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 3: Adherence by treatment group

Variables	Conservative N = XX	Liberal N = XX
Time spent in target SpO_2 ranges:		
Time in range (hours):		
Mean (SD)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Percentage of time points in range:		
Mean (SD)	XX (XX.X)	XX (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Adherence to the target SpO_2 range:		
SpO_2 below target range for two consecutive hours with no appropriate increase in flow rate, pressure or escalation of type of ventilation, or receiving 100% oxygen		
Number of events	XXX	XXX
Number (%) of patients	XX (XX.X)	XX (XX.X)
SpO_2 above target range for two consecutive hours, with no appropriate decrease in flow rate, pressure or de-escalation of type of ventilation,	XX	-
Number of events	XXX	-
Number (%) of patients	XX (XX.X)	-
Fully adherent		
Number (%) of patients	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 4: Adverse events by treatment group

Variables	Conservative N = XX	Liberal N = XX
Safety - Adverse events		
Severe lactic acidosis, n (%)	XX (XX.X)	XX (XX.X)
Cardiac ischaemia, n (%)	XX (XX.X)	XX (XX.X)
Acute Kidney injury, n (%)	XX (XX.X)	XX (XX.X)
Seizures, n (%)	XX (XX.X)	XX (XX.X)
Placeholder 1, n (%)	XX (XX.X)	XX (XX.X)
Placeholder 2, n (%)	XX (XX.X)	XX (XX.X)
Placeholder 3, n (%)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients

Table 5: Comparison of outcomes and support received by treatment group

Outcome	Conservative	Liberal		
	N = XXX	N = XXX	Effect estimates (95% CI)	P value
Length of PICU stay from randomisation (days):				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Median (IQR)	XX (XX, XX)	XX (XX, XX)		
Length of invasive ventilation (days)				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Median (IQR)	XX (XX, XX)	XX (XX, XX)		
Length of non-invasive respiratory support (days)				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Median (IQR)	XX (XX, XX)	XX (XX, XX)		
Ventilator-free days at day 30				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Days of cardiovascular support				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Median (IQR)	XX (XX, XX)	XX (XX, XX)		
Days of renal support				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Median (IQR)	XX (XX, XX)	XX (XX, XX)		
Days receiving sedatives				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X, X.X)	0.XXX
Median (IQR)	XX (XX, XX)	XX (XX, XX)		
PICU mortality				
n (%)	XX (XX.X)	XX (XX.X)	Risk ratio: X.XX (X.XX, X.XX) Absolute risk reduction: XX.X (XX.X, XX.X)	0.XXX

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 6: Confirmed diagnosis at discharge by treatment group

Variables	Conservative	Liberal	Total
	N = XXX	N = XXX	N = XXX
Discharge diagnosis			
Acute diagnosis, n (%)			
Severe sepsis / septic shock	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other infection	XX (XX.X)	XX (XX.X)	XX (XX.X)
Congenital heart disease	XX (XX.X)	XX (XX.X)	XX (XX.X)
Arrythmia	XX (XX.X)	XX (XX.X)	XX (XX.X)
Myocarditis / DCM	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other cardiac	XX (XX.X)	XX (XX.X)	XX (XX.X)
OSA	XX (XX.X)	XX (XX.X)	XX (XX.X)
DKA	XX (XX.X)	XX (XX.X)	XX (XX.X)
Inborn error	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other metabolic	XX (XX.X)	XX (XX.X)	XX (XX.X)
Leukaemia / lymphoma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Solid tumour	XX (XX.X)	XX (XX.X)	XX (XX.X)
Acute kidney injury	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other respiratory	XX (XX.X)	XX (XX.X)	XX (XX.X)
Multiple trauma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other trauma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Submersion	XX (XX.X)	XX (XX.X)	XX (XX.X)
Surgical - acute abdomen	XX (XX.X)	XX (XX.X)	XX (XX.X)
Complex or multiple congenital abnormalities	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neuromuscular disease	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asthma	XX (XX.X)	XX (XX.X)	XX (XX.X)
Aspiration pneumonia	XX (XX.X)	XX (XX.X)	XX (XX.X)
Pneumonia / LRTI	XX (XX.X)	XX (XX.X)	XX (XX.X)
Bronchiolitis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Croup	XX (XX.X)	XX (XX.X)	XX (XX.X)
Tracheitis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;

Figure 1a: Study flow diagram
CONSORT flow diagram

Figure 1b: Patients screened and recruited over time

Plots of number of patients screened and recruited per month and by site will be developed

Figure 2: Organ support over time
Plots of percentage of patients receiving the under listed support by treatment groups from days 0 to 15. Panels for:

- Cardiovascular (Continuous infusion of inotrope, Continuous infusion of vasodilator or Extracorporeal membrane oxygenation)
- Renal (Peritoneal dialysis, Haemofiltration, Haemodialysis, Plasma filtration or Plasma exchange)
- Sedatives or neuromuscular blockade

Figure 3: Interventions/Observations over time
Plots of mean (SD), unless indicated, by treatment group at hours 0 to 24, then after every 4 hours up to 72 hours, Panels for:

- SpO_2 (%) – shading for target ranges
- SpO_2 measurements in range (%)
- Flow rate (l/kg/min)
- Pressure (cmH_2O) - if CPAP
- Mean airway pressure (cmH_2O)
- FiO_2 (decimal)
- Receipt of invasive ventilation, non-invasive ventilation, high-flow humidified and none received (%)

Numbers at the foot of each figure will indicate the number of patients with measurements at each time point.