Randomised Multiple Centre Pilot Trial of Conservative versus Liberal Oxygenation Targets in Critically Ill Children (Oxy-PICU NCT03040570).

AUTHORS

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Oxy-PICU pilot MCRCT (n=119) demonstrates the feasibility of a definitive trial of oxygenation targets in critically ill children.

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Declaration of Interests

No conflicts of interest to declare.

Abstract

Background

Oxygen saturation monitoring during mechanical ventilation is standard worldwide. No randomised clinical trials have compared peripheral oxygen saturation targets for critically ill children.

Methods

We undertook an open, parallel-group randomised trial of children receiving mechanical ventilation with supplemental oxygen who were admitted as an emergency to one of three paediatric intensive care units. A 'research without prior consent' approach was employed. Children were randomly assigned to a liberal oxygenation group (SpO_2 targets >94%) or conservative oxygenation group (SpO_2 88-92% inclusive). Outcomes were measures of feasibility: recruitment rate, protocol adherence and acceptability, between group separation of SpO_2, and safety. The trial was registered before recruitment: ClinicalTrials.gov: NCT03040570.

Results

159 children met inclusion criteria of whom 119 (75%) were randomised between April and July 2017 representing a rate of 10 patients per month per site. Time to randomisation from first contact with an intensive care team was a mean (SD) of 1.9 (2.2) hours. Consent to continue in the study was obtained in 107 cases (90%); parents/legal representatives were supportive of the consent process.

The median (IQR) of time-weighted individual mean SpO_2 was 94.9% (92.6-97.1) in the conservative oxygenation group and 97.5% (96.2-98.4) in the liberal group (difference 2.7%, 95% confidence interval 1.3-4.0% $p<0.001$). Median (IQR) time-weighted individual mean FiO_2 was 0.28 (0.24-0.37) in the conservative group and 0.37 (0.30-0.42) in the liberal group (difference 0.08 0.03-0.13, $p<0.001$). There were no significant between group differences in length of stay, duration of organ support or mortality. Two pre-specified serious adverse events (cardiac arrests) occurred, both in the liberal oxygenation group.

Conclusion

A definitive clinical trial of peripheral oxygen saturation targets is feasible in critically ill children.

A main aim of resuscitation and intensive care is to maintain appropriate and safe levels of tissue oxygenation.[1-3] However, as it is difficult to directly measure tissue oxygen, estimates of peripheral oxygen saturation (SpO2) and arterial partial pressure are typically substituted. Mechanical ventilation with supplemental oxygen to maintain oxygen saturation and partial pressure is the most common organ support provided in paediatric intensive care units (PICU). Around 70% of UK PICU admissions are mechanically ventilated, 14-15,000 children annually. [4] Globally the figure is unknown but is in the hundreds of thousands. Despite these numbers there is no high-quality evidence from randomised clinical trials (RCTs) to inform the optimal level of oxygen saturation for critically ill children receiving mechanical ventilation.

Current practice relating to oxygen saturation targets varies widely in paediatric and adult intensive care units.[5, 6] Clinicians do prevent severe hypoxia wherever possible but beyond this there is little consensus. [7] Indeed, a fear of hypoxia leads many to target supra-normal values. We previously described supra-physiological levels of oxygenation as the norm on PICU; around one third of all recorded SpO_2 values are 100% and more than 60% of values were over 95%.[8]

Associations between high levels of arterial oxygenation and worse outcomes have been described post-cardiac arrest,[9, 10] during extra-corporeal oxygenation for congenital heart disease,[11] following stroke,[12] and in respiratory failure.[13] When added to the known risks of severe hypoxia, an 'U-shaped' relationship between arterial oxygenation and risk of death emerges.[3] We observed an excess mortality (both crude and adjusted) at extremes of oxygenation in 7410 critically ill children.[14] A complex U-shaped relationship between oxygenation and outcome is biologically feasible and may arise from the balance between harm from hypoxic injury at one extreme, and a combination of increased oxygen free radical damage and iatrogenic injury from more aggressive treatments at the other. [15]

Clinical trials of oxygen targets in extremely premature infants have shown that they influence survival

rates, retinopathy rates, and costs: large RCTs compared lower (85-89%) with higher SpO_2 targets (91-95%).[16, 17] Unexpectedly, an increased risk of death (relative risk 1.45; 95% confidence interval [CI], 1.15 to 1.84; p=0.002) was observed with the lower SpO_2targets.[17] In contrast, in adult critical illness, small trials indicate a possible benefit of lower oxygenation targets. [18, 19] No benefit or significant harm with supplemental oxygen has been demonstrated in adults with ST elevation myocardial infarction. [20-22]
The only paediatric trial data – in non-critically ill children with bronchiolitis – demonstrate equivalent safety of a SpO_2 target of >90% when compared to >94%. Later hospital discharges were seen with the higher target (ratio of length of stay 1.28, 95% CI 1.09-1.50, p=0·003). [23]

This pilot RCT was conducted to determine the safety and feasibility of a definitive multicentre RCT comparing current liberal targets for peripheral oxygen saturation with more conservative targets in critically ill children. The pilot RCT had the following objectives: 1) to test the willingness of clinicians to screen, recruit and randomise eligible patients; 2) to estimate the recruitment rate; 3) to test acceptability of the deferred consenting procedures and participant information; 4) to test, following randomisation, delivery of and adherence to, the intervention and demonstrate separation between the groups; 5) to test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event reporting; 6) to inform final selection of a patient-centred primary outcome measure; and 7) to estimate the characteristics of the selected patient-centred primary outcome measure to inform sample size estimation. The underlying hypothesis is that the harm of interventions to raise peripheral oxygen saturation to >94% exceeds the benefits of these interventions.

Methods

Study design and oversight

Oxy-PICU was a pragmatic, open, multi-centre RCT in infants and children accepted for emergency admission to one of three participating PICUs. Three units were selected as representing typical configurations for UK PICUs (general or combined general and cardiac units in general academic medical centres or within stand-alone children's hospitals).

The trial was coordinated by the Intensive Care National Audit & Research Centre (ICNARC) Clinical Trials Unit (CTU) and sponsored by Great Ormond Street Hospital for Children NHS Foundation Trust. Health Research Authority (HRA) (212228) and research ethics committee (16/SC/0617) approval were obtained. The trial was registered prior to recruitment of the first patient on ClinicalTrials.gov (NCT03040570) and the protocol published. [24] A trial steering committee (TSC), with a majority of independent members, and an independent data monitoring and ethics committee (DMEC) were convened to oversee the pilot trial on behalf of the sponsor.

A detailed description of the Methods including the study protocol has been published previously. [24]

Trial population and eligibility criteria

Inclusion criteria were: more than 38 weeks corrected gestational age and less than 16 years of age; emergency admission accepted to a participating PICU requiring mechanical ventilation within first 6 hours of face-to-face contact with PICU staff or transport team; receiving supplemental oxygen for abnormal gas exchange.

Mechanical ventilation was considered to include invasive and non-invasive ventilation and high-flow humidified oxygen.

Exclusion criteria were: death perceived as imminent; brain pathology/injury as primary reason for admission (e.g. traumatic brain injury, post-cardiac arrest, stroke, convulsive status epilepticus); 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 mechanical ventilation prior to this admission; or recruited to Oxy-PICU in a previous admission.

Screening & randomisation

Potentially eligible infants and children were screened against the inclusion/exclusion criteria by the transport team or PICU staff. Randomisation took place as soon as eligibility was confirmed including during transport. Participants were randomly allocated (1:1) via a secure web-based system to either the conservative (88-92%) or liberal (>94%) peripheral oxygen saturation (SpO_2) target group by a computer generated dynamic procedure (minimisation) with a random component (80% chance of allocation to the group that minimises imbalance). Minimisation was performed on: age (<12 months vs. ≥12 months); study site; primary reason for admission (lower respiratory tract infection vs. 'other'); and severity of abnormality of gas exchange (saturation to fraction of inspired oxygen (S/F) ratio <221 with PEEP >5 cmH_2O vs. other).

Trial interventions

Participants received supplemental oxygen and ventilator settings at the discretion of the treating clinical team with the aim of maintaining SpO_2 >94% in the liberal oxygenation group and between 88% and 92% (inclusive) in the conservative oxygen group until mechanical ventilation was discontinued during the PICU admission. All other care was determined by the clinical team primarily responsible for the participant's care. Data on oxygenation parameters and ventilator settings were recorded hourly from randomisation to 24 hours, every four hours from 24 to 120 hours (Day 6) and every 12 hours from Day 6 to the end of ventilation.

Consent procedures

We employed a 'research without prior consent' approach as is appropriate in emergency situations where any delay in commencing treatment allocation may be detrimental and when the treatments being compared are within the range of normal practice. A member of the research team approached the

parents/legal representatives as soon as practical after randomisation to discuss the study, to provide a participant information sheet (PIS) (Supplementary Material) and to seek consent for continued inclusion in the study. If the participant was discharged or died prior to their parents/legal representatives being approached, then they were approached by an appropriate team member at a later point either in person or by post with an option to opt out from the study at this point. The acceptability of this consent process was assessed with a 12-question multiple-choice questionnaire provide to parents/legal representatives following the approach for consent (Supplementary Material).

Outcome Measures and Statistics

As it was a pilot RCT, no formal sample size calculations were performed, instead a sample size of 120 was determined to be adequate to estimate candidate patient-centred outcome measures to a necessary degree of precision and to test the trial processes.

The following outcome measures were used to assess the specified objectives. Objective 1: the proportion of eligible patients recruited (target 50%); and distribution of time to randomisation. Objective 2: the number of eligible patients recruited per month. Objective 3: Proportion of parents/legal representatives refusing deferred consent. Objective 4: total time in SpO_2 target range and percentage of time in range, time-weighted mean SpO_2, and time-weighted mean FiO_2. Objectives 5-7: characteristics and completeness of potential primary endpoints for a definitive study including: length of PICU stay, length of invasive ventilation, ventilator-free days at day 30, duration of organ support, and PICU mortality; and observed serious adverse events.

All analyses were carried out on an intention to treat (ITT) basis. Continuous variables were summarized as mean (standard deviation) and median (interquartile range) whilst categorical variables were summarized as number (percentage).

Results

Between April and July 2017, 332 patients were screened and deemed to meet the inclusion criteria. Of these, 170 patients met one or more of the exclusion criteria and a further 40 were deemed eligible but were not randomised. Overall, 122 were randomised to the pilot RCT (Figure 1). Three patients were randomised in error. Two were immediately removed from the study before receiving the intervention (one outside of age range, one randomised previously). One was removed from the study within hours after being recognised as meeting the 'brain pathology as the main precipitant to admission' exclusion criterion. Therefore, 74.8% (119/159) of eligible patients were appropriately randomised at a recruitment rate of 10 patients per month per site. Time to randomisation from first contact was a mean (SD) of 1.9 (2.2) hours. Baseline characteristics were balanced between the arms (Table 2) Consent for continuation in the study was subsequently declined in 9/119 patients (7.6%). Eight of these cases were at a single study site. Three further cases (3/119, 2.5%), did not continue in the study because we were unable to seek consent (a suitable translator was not available for one family and two children were subject to care orders). Forty-four (44/116 38%) completed consent questionnaires were returned, 40/44 (91%) reported being satisfied with the consent process while the remainder (4/44, 9%) were neither satisfied nor dissatisfied (Table 3). Full survey results including free text comments are available in the supplementary material (Tables S1 and S2). 107 out of the 119 (89.9%) correctly randomised patients were therefore analysed to evaluate objectives 4-7.

The median (IQR) of time-weighted individual mean SpO_2 was 94.9% (92.6-97.1) in the conservative group and 97.5% (96.2-98.4) in the liberal group (difference in medians of 2.7, 95% confidence interval (CI) 1.3-4.0%, p<0.001) for the full duration of mechanical ventilation. Values for the first 24 hours were similar: conservative 94.7% (93-97) vs. liberal 97.4% (96.3-98.2), (difference 2.8, 95% CI 1.5-4.0, p<0.001. (Figure 2) The median (IQR) time-weighted individual FiO_2 was 0.28 (0.24-0.37) in the conservative group and 0.37 (0.30-0.42) in the liberal group (difference 0.08, 95% CI 0.03-0.13, p<0.001) for the full duration of mechanical ventilation. The median (IQR) FiO_2 values in the first 24 hours were slightly higher: conservative 0.29 (0.25-0.37) and liberal 0.40 (0.31-0.5), (difference 0.11, 95% CI 0.05-0.17, p<0.001).

Of all recorded FiO_2 values, 36.4% (804/2210) were 0.21 in the conservative group compared to 13.0% (306/2347) in the liberal group (Chi-squared p<0.001). In the first 24 hours following contact with PICU or the transport team, study participants in the conservative oxygenation group spent a median (IQR) of 4.5 (1.0-10) hours in the target range compared to 22 (19-23) hours in the liberal group.

Candidate patient centred outcomes had high completion rates and were similar between groups. Detailed characteristics are provided in Table 4. Two pre-specified serious adverse events (cardiac arrests) occurred, both in the liberal oxygenation group.

Discussion

In this multiple centre, parallel-group, pilot RCT, we investigated the feasibility of conducting a large-scale trial comparing conservative oxygenation (SpO_2 88-92%) with liberal oxygenation (SpO_2 >94%) in critically ill children receiving mechanical ventilation.

We observed that the eligibility criteria were effective in identifying patients and that clinicians were prepared to randomise these patients. Our initial estimates of the number of emergency admissions who met these criteria were shown to be very conservative with recruitment being completed in approximately two-thirds of the planned study time. Indeed, our study may have underestimated the true potential recruitment rate further because the study period did not include any winter months during which admissions in acute respiratory failure predominate. The randomisation processes were timely and effective with short intervals between first contact and randomisation. The high rates of recruitment of eligible patients and low rates of consent being declined are comparable with other emergency studies in critically ill children. Families' feedback of the consent process was both overwhelmingly supportive and in line with our recent findings in the Fluids in Shock study. [25] The variability in consent rates by institution will inform on our site training for approaching families in a larger study.

The protocol achieved separation of the groups in terms of SpO_2 and FiO_2 values. Our SpO_2 values were almost identical both in values and separations to those achieved in the CLOSE study reported by the ANZIC group in critically ill adults. [18] However, adherence to oxygenation target range was poor in the conservative group. This was especially clear in the first few hours after randomisation. This may reflect the lack of an option to reduce FiO_2 below 0.4 on many paediatric transport ventilators. In addition, many children clinically improved rapidly so that an SpO_2 goal of 88-92% was not achievable because they were already breathing air. It may also be true that some bedside staff preferred values of 100% based on previous usual practice especially during episodes of chest physiotherapy or other procedures. The pre-randomisation baseline SpO_2 values of 99% reinforce the extent to which normal practice is for very liberal SpO_2 values.

Further work with high-resolution (q5 sec) analysis of SpO_2 data is in progress to understand this behaviour with a view to refining the protocol further. A higher baseline threshold FiO_2 for inclusion (e.g. >0.50), and a recommendation for setting an upper SpO_2 alarm limit are simple protocol refinements that may improve adherence further without a major impact on the other trial processes.

Since this study was planned, a number of trials of oxygenation strategies in adults have reported or opened for recruitment. The HYPER2S trial in adult with septic shock employed a factorial design comparing an FiO_2 1.0 with an SpO_2 target of 88-95% alongside hypertonic vs. isotonic volume resuscitation. It was stopped prematurely for safety concerns of increased weakness and atelectasis in the hyperoxia group with a trend to increased mortality. [26] The single centre Oxygen-ICU study observed reduced mortality with modestly reduced oxygenation targets (SpO_2 94-98% vs. 97-100%).[19] A number of larger studies are currently recruiting including: Evaluating the effects of two approaches to oxygen therapy in Intensive Care Unit patients requiring life support (ICU-RO_X) ACTRN 12615000957594 by the ANZICS group, and Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) in Denmark NCT03174002; Optimal Oxygenation in the Intensive Care Unit (O2-ICU) in Holland NCT02321072; Liberal Oxygenation Versus Conservative Oxygenation in ARDS (LOCO2) in France NCT02713451 and Targeted oxygen therapy in

mechanically ventilated critically ill patients (TO2T) NCT03287466 in the UK. Maitland and colleagues are conducting a large study of oxygen treatment thresholds combined with a comparison of high flow vs. low flow oxygen delivery in east Africa, ISRCTN15622505. [27]

Our study shares a number of weaknesses with the majority of these trials. Exclusion of cases with acute encephalopathy or congenital cardiac disease limits the generalisability of any findings to a subset of critically-ill children. These were felt to be necessary because of our work scoping current practice and equipoise. [7] We did not attempt to blind clinical staff to the group allocation. Our pragmatic approach means that clinicians were free to adopt different haemodynamic goals, temperature control strategies or transfusion thresholds that might alter the balance between oxygen delivery and consumption independent of the SpO_2 targets. These multiple interactions may only be tractable with more complex adaptive trial designs.[28] In addition, as a feasibility study we cannot make any conclusions on the effectiveness of conservative oxygenation.

There are also several strengths of Oxy-PICU beyond it being the first report of a randomised comparison of conservative and liberal oxygenation strategies in critically ill children. We have demonstrated a high degree of engagement of clinical staff with the protocol across different units and transport teams. The trial processes were acceptable to parents/legal representatives. No safety issues were identified and there were trends across the clinical outcomes for shorter durations of organ support in the conservative group that might be suitable as outcome measures in a full trial.

Although the choice of primary outcome measure for a definitive trial will involve consultation with patients and families and considerations of cost, timings and competing studies, our data permit sample size estimations. For example a 'ventilator-free days' outcome with 90% power to detect a 1.25 day difference in ventilation and no effect on mortality would require a total of 2014 patients. These pilot data support the feasibility of a trial on this scale in critically-ill children.

Conclusion

This Oxy-PICU study has demonstrated that it is feasible to conduct a large pragmatic clinical trial of conservative vs. liberal oxygenation in critically ill children. Considerations for a full trial include addition of an FiO_2 threshold for inclusion, and a recommendation for an upper SpO_2 alarm limit in the conservative group.

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Figures

Figure 1 Flow of participants through the pilot randomised clinical trial

Figure 2. Distribution of SpO_2 and FiO_2 by treatment group.
The percentage of time at each SpO_2 over entire PICU stay (a, b) and median (IQR) SpO_2 (c, d) and FiO_2 (e) measurements at individual timepoints for the first 72 hours following randomisation are shown. Left hand panels (a, c, e) show all mechanically ventilated timepoints whereas right hand panels (b, d) show only SpO_2 values in children mechanically ventilated with FiO_2>0.21 (b, d). Shaded areas illustrate the treatment group target SpO_2 ranges.

Figure S1 SpO2 and FiO2 Distributions by treatment group over the first 7 days of ventilation
Median (IQR) SpO_2 (a, b) and FiO_2 (c) measurements at individual timepoints for the first 168 hours following randomisation are shown. Left hand panels (a, b) show all mechanically ventilated timepoints whereas the right hand panel (c) shows only SpO_2 values in children mechanically ventilated with FiO_2>0.21 Shaded areas illustrate the treatment group target SpO_2 ranges.

Tables

Table 1 Number of patients randomised and consented, and time to randomisation, by treatment group

Table 2 Baseline characteristics by treatment group

Table 3 Family survey responses regarding the consent process (N=44).

Table 4. Clinical outcomes by treatment group

Table S1 Family consent survey reasons for providing consent (N=42)

Table S2 Family survey consent reasons for not providing consent (N=2)

Table 1 Number of patients randomised and consented, and time to randomisation, by treatment group

Variables	Conservative	Liberal	Total
Number of patients randomised,			
n	61	61	122
Number randomised in error, n (% of randomised)			
n (%)	1/61 (1.6)	2/61 (3.2)	3/122 (2.4)
Number unable to seek consent, n (% of randomised)			
n (%)	2/61 (3.3)	1/61 (1.6)	3/122 (2.4)
Consent declined, n (% of randomised)			
n (%)	4/61 (6.6)	5/61 (8.2)	9/122 (7.3)
Time to randomisation from first contact (hours)			
Median (IQR)	1.4 (0.8, 2.3)	1.6 (0.8, 2.7)	1.5 (0.8, 2.5)

Table 2 Baseline characteristics of patients n: Number of patients; %: Percentage of patients; N: Total number of patients; SD: Standard deviation; IQR: Inter-quartile range; GOSH: Great Ormond Street Hospital, SMH: St Mary's Hospital, UHS: University Hospital Southampton.

	Conservative	Liberal	Total
	N = 54	N = 53	N = 107
Age (years) Median (IQR)	1.9 (0.4,5.0)	0.8 (0.1,2.0)	1.1 (0.1,4.0)
Age group, n (%)			
< 1 year	19/54 (35.2)	29/53 (54.7)	48/107 (44.9)
1 year	8/54 (14.8)	10/53 (18.9)	18/107 (16.8)
2 to 4 years	11/54 (20.4)	7/53 (13.2)	18/107 (16.8)
5 to 9 years	11/54 (20.4)	3/53 (5.7)	14/107 (13.1)
10 to 16 years	5/54 (9.3)	4/53 (7.5)	9/107 (8.4)
Female (%)	33/54 (61.1)	24/53 (45.3)	57/107 (53.3)
Weight (kg) Median (IQR)	12.0 (5.8,20.0)	8.0 (3.7,13.7)	9.5 (4.2,17.0)
Mode of Respiratory Support n (%)			
Invasive ventilation	47/54 (87.0)	47/53 (88.7)	94/107 (87.8)
Non-invasive ventilation	3/54 (5.6)	0/53 (0.0)	3/107 (2.8)
High-flow humidified oxygen	4/54 (7.4)	6/53 (11.3)	10/107 (9.3%)
PIM2 High Risk Comorbidities, n (%)			
Cardiac arrest before PICU admission	0/54 (0.0)	1/53 (1.9)	1/107 (0.9)
Cardiomyopathy or myocarditis	1/54 (1.9)	0/53 (0.0)	1/107 (0.9)
Severe combined immune deficiency	1/54 (1.9)	0/53 (0.0)	1/107 (0.9)
Leukaemia or lymphoma after first induction	1/54 (1.9)	1/53 (1.9)	2/107 (1.9)
Neurodegenerative disorder	1/54 (1.9)	0/53 (0.0)	1/107 (0.9)
Bone marrow transplant recipient	1/54 (1.9)	1/53 (1.9)	2/107 (1.9)
PIM2r score: Median IQR	1.0 (0.8,1.6)	1.2 (0.8,2.0)	1.1 (0.8,1.8)
Acute diagnosis, n (%)			
Severe sepsis / septic shock	9/54 (16.7)	5/53 (9.4)	14/107 (13.1)
Other infection	4/54 (7.4)	0/53 (0.0)	4/107 (3.7)

Arrythmia	0/54 (0.0)	1/53 (1.9)	1/107 (0.9)
Myocarditis / DCM	1/54 (1.9)	0/53 (0.0)	1/107 (0.9)
Other cardiac	0/54 (0.0)	0/53 (0.0)	0/107 (0.0)
OSA	0/54 (0.0)	1/53 (1.9)	1/107 (0.9)
DKA	1/54 (1.9)	0/53 (0.0)	1/107 (0.9)
Other metabolic	0/54 (0.0)	2/53 (3.8)	2/107 (1.9)
Solid tumour	0/54 (0.0)	1/53 (1.9)	1/107 (0.9)
Acute kidney injury	0/54 (0.0)	0/53 (0.0)	0/107 (0.0)
Other respiratory	8/54 (14.8)	13/53 (24.5)	21/107 (19.6)
Trauma	0/54 (0.0)	1/53 (1.9)	1/107 (0.9)
Surgical - acute abdomen	0/54 (0.0)	3/53 (5.7)	3/107 (2.8)
Complex or multiple congenital abnormalities	1/54 (1.9)	0/53 (0.0)	1/107 (0.9)
Asthma	6/54 (11.1)	3/53 (5.7)	9/107 (8.4)
Aspiration pneumonia	4/54 (7.4)	3/53 (5.7)	7/107 (6.5)
Pneumonia / LRTI	13/54 (24.1)	13/53 (24.5)	26/107 (24.3)
Bronchiolitis	6/54 (11.1)	6/53 (11.3)	12/107 (11.2)
Croup	1/54 (1.9)	1/53 (1.9)	2/107 (1.9)
Physiology at Presentation			
Arterial PaO_2 (kPa):	N = 30	N = 28	N = 58
Median (IQR)	14.6 (8.0,21.2)	10.6 (8.4,14.9)	11.6 (8.4,20.8)
FiO_2:	N = 54	N = 53	N = 107
Median (IQR)	0.5 (0.4,0.8)	0.5 (0.4,0.8)	0.5 (0.4,0.8)
Base excess (mmol l^{-1}):	N = 43	N = 44	N = 87
Mean (SD)	5.6 (5.3)	6.6 (5.3)	6.1 (5.3)
Lactate (mmol l^{-1})	N = 41	N = 43	N = 84
Median (IQR)	1.5 (0.9,3.4)	1.1(0.8,2.2)	
SpO_2 (%):	N = 54	N = 53	N = 107
Median (IQR)	99 (97,100)	99 (98,100)	99 (97,100)
SBP (mmHg):	N = 52	N = 50	N = 102
Mean (SD)	97.0 (22.2)	90.0 (23.2)	93.6 (22.8)
Mean Airway Pressure:	N = 14	N = 9	N = 23
Mean (SD)	10.6 (2.3)	9.7 (1.3)	10.3 (2.0)

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

SD: Standard deviation; IQR: Inter-quartile range

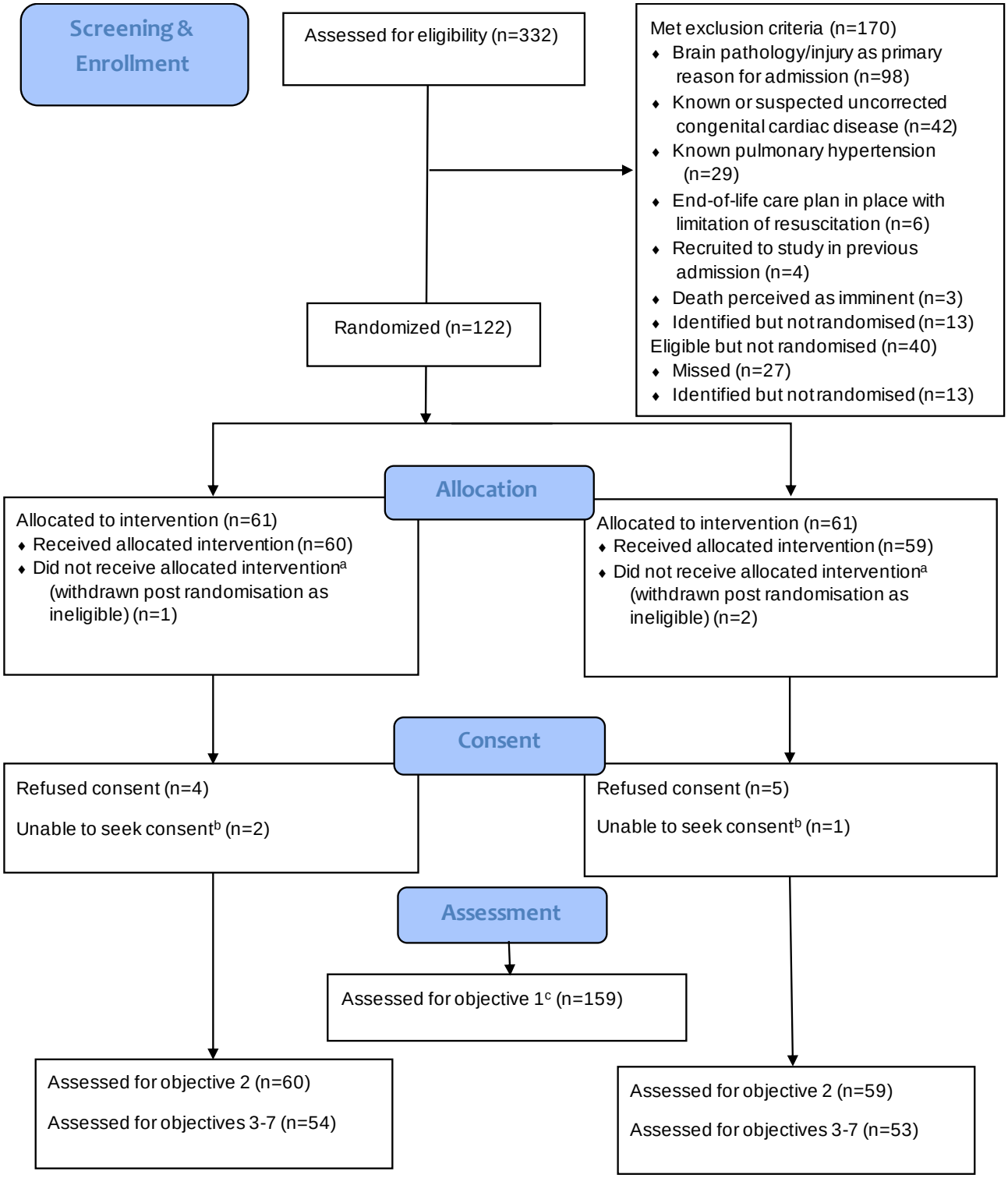
Table 3 Family survey responses regarding the consent process (N=44). Responses provided by child's mother in 34 cases (77%), father in 9 cases (20%) and Grandparent in 1 case (2%)

Statement	Agree n (%)		Neither agree nor disagree n (%)		Disagree n (%)	
a. The doctor or nurse checked that it was a convenient time to discuss research before discussing Oxy-PICU	43	98%	0	0%	1	2%
b. I was initially surprised to find out that my child had already been entered into Oxy-PICU	16	36%	15	34%	13	30%
c. The information I received about Oxy-PICU was clear and straightforward to understand	43	98%	1	2%	0	0%
d. I understood why consent for my child's participation in Oxy-PICU was sought after the treatment had been given	41	93%	1	2%	2	5%
e. I had enough opportunity to ask questions about Oxy-PICU	44	100%	0	0%	0	0%
f. I was satisfied with the deferred consent process for Oxy-PICU	40	91%	4	9%	0	0%
g. It was difficult to take in the information I was given about Oxy-PICU	3	7%	7	16%	34	77%
h. It was difficult to make a decision about Oxy-PICU	5	11%	6	14%	33	75%
i. I made this decision	42	95%	2	5%	0	0%
j. Someone took this decision away from me	1	2%	2	5%	41	93%
k. I was not in control of this decision	7	17%	2	5%	33	79%
l. The decision about the research was inappropriately influenced by others	1	2%	2	5%	41	93%

Table 4 Clinical outcomes by treatment group

Outcome	Conservative N = 54	Liberal N = 53	Effect estimates (95%CI)	P value
Length of PICU stay from randomisation (days):				
Median (IQR)	5 (4,8)	6 (4,11)	Median difference 1 (-0.8, 2.9)	0.292
Length of invasive ventilation (days)				
Median (IQR)	3 (2,6)	3 (2,6)	Median difference: 0 (-1.64, 1.64)	1.0
Ventilator-free days at day 30				
Mean (SD)	23.1 (8.1)	22.8 (8.2)	Median difference: 0.1 (-1.6, 1.6)	1.0
Median (IQR)	26.0 (23.0, 28.0)	26 (23, 27)		
Days of cardiovascular support				
Median (IQR)	0, (0,1)	0, (0,2)	Median difference: 0 (-0.5, 0.5)	1.0
Days of renal support				
Median (IQR)	0 (0, 0)	0 (0, 0)	Median difference: -	-
Days receiving sedatives				
Median (IQR)	3 (2,6)	4 (2,7)	Median difference: 1 (-0.6, 2.6)	0.229
PICU mortality				
n (%)	4/54 (7.4)	4/53 (7.5)	Risk ratio: 0.98 (0.26, 3.72) Absolute risk reduction: -0.1 (-10.1, 9.8)	0.978

Figure 1. Flow of participants through the pilot randomised clinical trial



a Three patients were withdrawn following randomisation in error: one was out of age range, one had previously been recruited to the study and one met the brain pathology/injury exclusion criterion.

b Unable to seek consent in three cases: two children were subject to child protection care orders and one for whom no suitable translator was available for the family.

c Includes both randomised and eligible and not randomised patients. Excludes three patients withdrawn after randomisation

Figure 2. Distribution of SpO_2 and FiO_2 by treatment group.

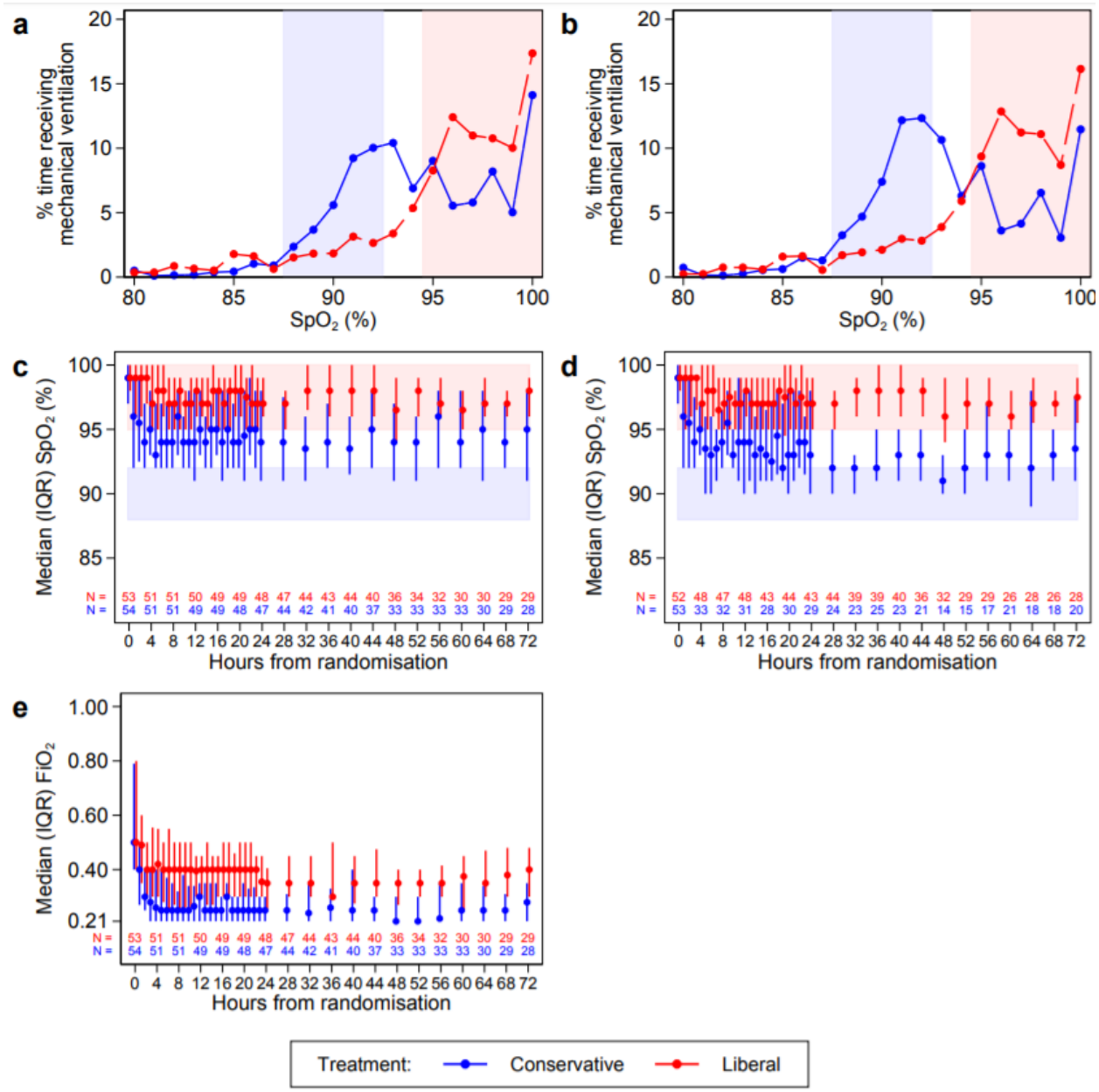


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Table S1 Family consent survey reasons for providing consent (N=42)

Reason for consent	Identified as a reason (n=41)		Identified as the main reason (n=15*)	
1. To help my child	25	61%	3	16%
2. To help other children in the future	40	98%	10	53%
3. I felt that medical studies like Oxy-PICU are important	38	93%	6	32%
4. Because I trusted the doctor or nurse who explained Oxy-PICU	25	61%	0	0%
5.The treatment had already been given to my child	8	20%	0	0%
6. My child recovered	4	10%	0	0%
7. I didn't feel comfortable saying no to the nurse or doctor who explained	0	0%	0	0%
8. If the research is not done other babies/ children may suffer in the future, WE NEED RESEARCH	1	2%	0	0%

*2 people chose 3 main reasons (1, 2 and 3)

Other comments

- My husband cannot read so when given the paper information he was unable to read it. He does not like telling people he can't read. However, the doctor explained it well. It maybe something to bare in mind. However, there were lots of opportunities to ask questions.
- To help future treatment of children is definitely a good thing as long as the care of my child is not hindered at all.
- You're doing a great job
- If by using my child's data which has already been logged to help others in the future, and my child is not at risk, I'm happy.
- Research nurse was very helpful and went through everything
- No, happy with the process

Table S2 Family survey consent reasons for not providing consent (N=2)

Those that did not consent

Statement	Agree n (%)		Neither agree nor disagree n (%)		Disagree n (%)	
a. The doctor or nurse checked that it was a convenient time to discuss research before discussing Oxy-PICU	2	100%	0	0%	0	0%
b. I was initially surprised to find out that my child had already been entered into Oxy-PICU	2	100%	0	0%	0	0%
c. The information I received about Oxy-PICU was clear and straightforward to understand	2	100%	0	0%	0	0%
d. I understood why consent for my child's participation in Oxy-PICU was sought after the treatment had been given	2	100%	0	0%	0	0%
e. I had enough opportunity to ask questions about Oxy-PICU	2	100%	0	0%	0	0%
f. I was satisfied with the deferred consent process for Oxy-PICU	1	50%	1	50%	0	0%
g. It was difficult to take in the information I was given about Oxy-PICU	0	0%	1	50%	1	50%
h. It was difficult to make a decision about Oxy-PICU	1	50%	0	0%	1	50%
i. I made this decision	2	100%	0	0%	0	0%
j. Someone took this decision away from me	0	0%	0	0%	2	100%
k. I was not in control of this decision	0	0%	0	0%	2	100%
l. The decision about the research was inappropriately influenced by others	0	0%	0	0%	2	100%

Other comments: Reason for non-consent: I didn't want to put any extra exertion on his treatment/body no matter how small in the hope it helps his recovery (liberal group). (1 missing)

Supplementary Figure S1 SpO2 and FiO2 Distributions by treatment group over the first 7 days of ventilation