



# Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial

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## Abstract

**Background:** Oxygen saturation monitoring for children receiving respiratory support is standard worldwide. No randomised clinical trials have compared peripheral oxygen saturation (SpO<sub>2</sub>) targets for critically ill children. The harm of interventions to raise SpO<sub>2</sub> to > 94% may exceed their benefits.

**Methods:** We undertook an open, parallel-group randomised trial of children > 38 weeks completed gestation and < 16 years of age receiving invasive or non-invasive respiratory support and supplemental oxygen who were admitted urgently 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<sub>2</sub> targets > 94%) or a conservative oxygenation group (SpO<sub>2</sub> = 88–92% inclusive). Outcomes were measures of feasibility: recruitment rate, protocol adherence and acceptability, between-group separation of SpO<sub>2</sub> and safety. The Oxy-PICU trial was registered before recruitment: ClinicalTrials.gov identifier NCT03040570.

**Results:** A total of 159 children met the inclusion criteria, of whom 119 (75%) were randomised between April and July 2017, representing a rate of 10 patients per month per site. The mean time to randomisation from first contact with an intensive care team was 1.9 (SD 2.2) h. Consent to continue in the study was obtained in 107 cases (90%); the children's parents/legal representatives were supportive of the consent process. The median (interquartile range, IQR) of time-weighted individual mean SpO<sub>2</sub> 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 (95% CI) 1.3–4.0%, *p* < 0.001]. Median (IQR) time-weighted individual mean FiO<sub>2</sub> 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). There were no significant between-group differences in length of stay, duration of organ support or mortality. Two prespecified 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.

**Keywords:** PICU respiratory failure, Oxygenation, Clinical trial

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The Oxy-PICU trial has been registered at ClinicalTrials.gov (NCT03040570).

## Introduction

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 (SpO<sub>2</sub>) and arterial partial pressure are typically substituted. Invasive 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 invasively mechanically ventilated, amounting to 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 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<sub>2</sub> values were 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, a ‘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, with large RCTs comparing lower (85–89%) with higher SpO<sub>2</sub> targets (91–95%) [16, 17]. Unexpectedly, an increased risk of death [relative risk 1.45; 95% confidence interval (CI), 1.15–1.84;  $p=0.002$ ] was observed with the lower SpO<sub>2</sub> targets [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<sub>2</sub> 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 the 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 and Research Centre Clinical Trials Unit and sponsored by Great Ormond Street Hospital for Children NHS Foundation Trust. Health Research Authority (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, with a majority of independent members, and an independent data monitoring and ethics committee 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; within the first 6 h of face-to-face contact with PICU staff or transport team; an emergency admission accepted to a participating PICU requiring invasive or non-invasive respiratory support (including: invasive mechanical ventilation, non-invasive ventilation or high-flow humidified oxygen therapy), and 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 and 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<sub>2</sub>) 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 ratio <221 with PEEP/CPAP >5 cm H<sub>2</sub>O 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<sub>2</sub> >94% in the liberal oxygenation group and between 88 and 92% (inclusive) in the conservative oxygen group until respiratory support 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 h, every 4 h from 24 to 120 h (day 6) and every 12 h 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 (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 provided 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: the proportion of parents/legal representatives refusing deferred consent. Objective 4: total time in SpO<sub>2</sub> target range and percentage of time in range, time-weighted mean SpO<sub>2</sub>, and time-weighted mean FiO<sub>2</sub>. 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.

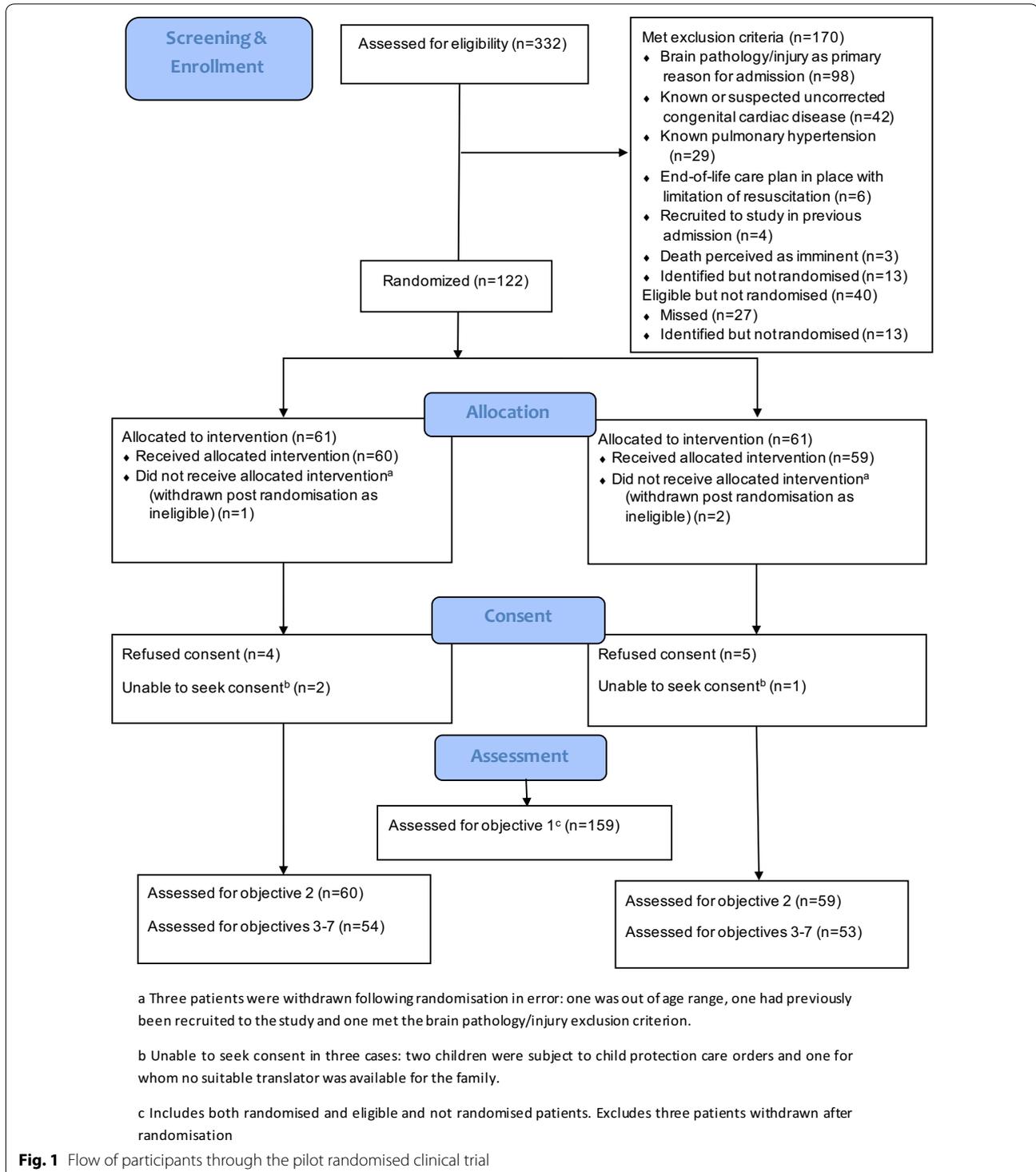
All analyses were carried out on an intention to treat basis. Continuous variables were summarised as mean (standard deviation) and median (interquartile range), while categorical variables were summarised as number (percentage).

### 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 (Fig. 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



**Table 1 Baseline characteristics of patients by treatment group**

	Conservative <i>n</i> = 54	Liberal <i>n</i> = 53
Age (years) median (IQR)	1.9 (0.4,5.0)	0.8 (0.1,2.0)
Age group (years), <i>n</i> (%)		
< 1	19/54 (35.2)	29/53 (54.7)
1	8/54 (14.8)	10/53 (18.9)
2–4	11/54 (20.4)	7/53 (13.2)
5–9	11/54 (20.4)	3/53 (5.7)
10–16	5/54 (9.3)	4/53 (7.5)
Female (%)	33/54 (61.1)	24/53 (45.3)
Weight (kg) median (IQR)	12.0 (5.8, 20.0)	8.0 (3.7, 13.7)
Mode of respiratory support, <i>n</i> (%)		
Invasive ventilation	47/54 (87.0)	47/53 (88.7)
Non-invasive ventilation	3/54 (5.6)	0/53 (0.0)
High-flow humidified oxygen	4/54 (7.4)	6/53 (11.3)
PIM2 high-risk comorbidities, <i>n</i> (%)		
Cardiac arrest before PICU admission	0/54 (0.0)	1/53 (1.9)
Cardiomyopathy or myocarditis	1/54 (1.9)	0/53 (0.0)
Severe combined immune deficiency	1/54 (1.9)	0/53 (0.0)
Leukaemia or lymphoma after first induction	1/54 (1.9)	1/53 (1.9)
Neurodegenerative disorder	1/54 (1.9)	0/53 (0.0)
Bone marrow transplant recipient	1/54 (1.9)	1/53 (1.9)
PIM2r score: median IQR	1.0 (0.8, 1.6)	1.2 (0.8, 2.0)
Acute diagnosis, <i>n</i> (%)		
Severe sepsis/septic shock	9/54 (16.7)	5/53 (9.4)
Other infection	4/54 (7.4)	0/53 (0.0)
Arrhythmia	0/54 (0.0)	1/53 (1.9)
Myocarditis/DCM	1/54 (1.9)	0/53 (0.0)
Other cardiac	0/54 (0.0)	0/53 (0.0)
OSA	0/54 (0.0)	1/53 (1.9)
DKA	1/54 (1.9)	0/53 (0.0)
Other metabolic	0/54 (0.0)	2/53 (3.8)
Solid tumour	0/54 (0.0)	1/53 (1.9)
Acute kidney injury	0/54 (0.0)	0/53 (0.0)
Other respiratory	8/54 (14.8)	13/53 (24.5)
Trauma	0/54 (0.0)	1/53 (1.9)
Surgical—acute abdomen	0/54 (0.0)	3/53 (5.7)
Complex or multiple congenital abnormalities	1/54 (1.9)	0/53 (0.0)
Asthma	6/54 (11.1)	3/53 (5.7)
Aspiration pneumonia	4/54 (7.4)	3/53 (5.7)
Pneumonia/LRTI	13/54 (24.1)	13/53 (24.5)
Bronchiolitis	6/54 (11.1)	6/53 (11.3)
Croup	1/54 (1.9)	1/53 (1.9)
Physiology at presentation		
Arterial PaO <sub>2</sub> (kPa)	<i>n</i> = 30	<i>n</i> = 28
Median (IQR)	14.6 (8.0, 21.2)	10.6 (8.4, 14.9)
FiO <sub>2</sub>	<i>n</i> = 54	<i>n</i> = 53
Median (IQR)	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)

**Table 1 continued**

	Conservative <i>n</i> = 54	Liberal <i>n</i> = 53
Base excess (mmol l <sup>-1</sup> )	<i>n</i> = 43	<i>n</i> = 44
Mean (SD)	5.6 (5.3)	6.6 (5.3)
Lactate (mmol l <sup>-1</sup> )	<i>n</i> = 41	<i>n</i> = 43
Median (IQR)	1.5 (0.9, 3.4)	1.1 (0.8, 2.2)
SpO <sub>2</sub> (%)	<i>n</i> = 54	<i>n</i> = 53
Median (IQR)	99 (97, 100)	99 (98, 100)
SBP (mmHg)	<i>n</i> = 52	<i>n</i> = 50
Mean (SD)	97.0 (22.2)	90.0 (23.2)
Mean airway pressure	<i>n</i> = 14	<i>n</i> = 9
Mean (SD)	10.6 (2.3)	9.7 (1.3)

% Percentage of patients, *N* total number of patients *SD* standard deviation, *IQR* inter-quartile range

from first contact was a mean (SD) of 1.9 (2.2) h. Baseline characteristics were balanced between the arms (Table 1). 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 2). Full survey results including free text comments are available in the supplementary material (Tables S2 and S3). A total of 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<sub>2</sub> 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% CI 1.3–4.0%, *p* < 0.001) for the full duration of mechanical ventilation. Values for the first 24 h were similar: conservative 94.7% (93–97) versus liberal 97.4% (96.3–98.2), (difference 2.8, 95% CI 1.5–4.0, *p* < 0.001) (Fig. 2). The median (IQR) time-weighted individual FiO<sub>2</sub> 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<sub>2</sub> values in the first 24 h 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<sub>2</sub> 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 h following contact with PICU or the transport team,

**Table 2 Family survey responses regarding the consent process (n = 44)**

Statement	Agree	Neither agree nor disagree	Disagree
	n (%)	n (%)	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%)

Responses provided by child's mother in 34 cases (77%), father in 9 cases (20%) and grandparent in 1 case (2%)

study participants in the conservative oxygenation group spent a median (IQR) of 4.5 (1.0–10) h in the target range compared to 22 (19–23) h in the liberal group.

Candidate patient-centred outcomes had high completion rates and were similar between groups. Detailed characteristics are provided in Table 3. 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<sub>2</sub> 88–92%) with liberal oxygenation (SpO<sub>2</sub> > 94%) in critically ill children receiving respiratory support.

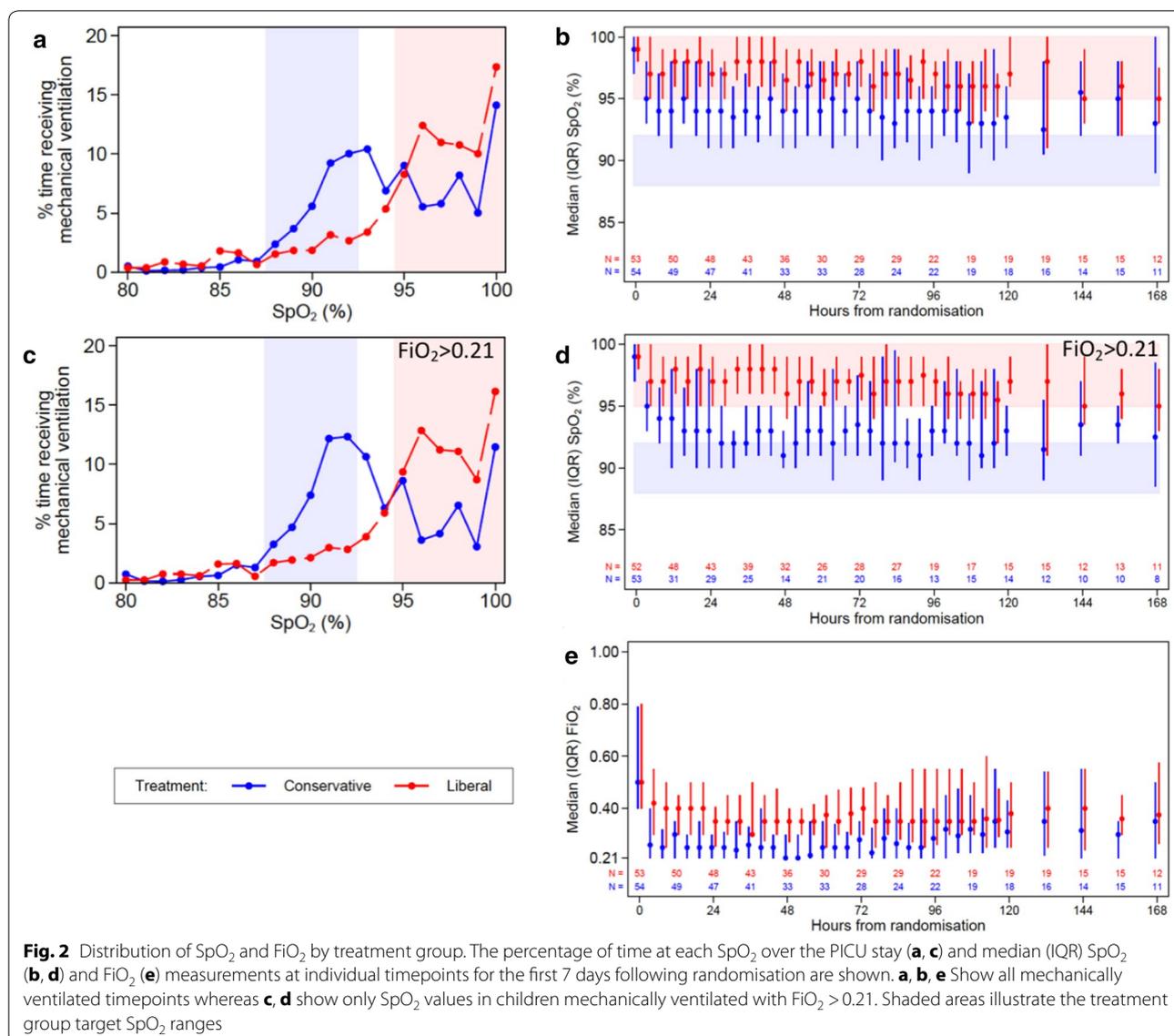
We observed that the eligibility criteria were effective in identifying patients and that clinicians were prepared to randomise these patients. Our initial estimates of the number of emergency admissions who met these criteria were shown to be very conservative, with recruitment being completed in approximately two-thirds of the planned study time. Indeed, our study may have further underestimated the true potential recruitment rate 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 our site training for approaching families in a larger study.

The protocol achieved separation of the groups in terms of SpO<sub>2</sub> and FiO<sub>2</sub> values. Our SpO<sub>2</sub> 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 the 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<sub>2</sub> below 0.4 on many paediatric transport ventilators. In addition, many children clinically improved rapidly so that an SpO<sub>2</sub> 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<sub>2</sub> values of 99% reinforce the extent to which normal practice is for very liberal SpO<sub>2</sub> values.

Further work with high-resolution (q5 s) analysis of SpO<sub>2</sub> data is in progress to understand this behaviour, with a view to further refining the protocol. A higher baseline threshold FiO<sub>2</sub> for inclusion (e.g. >0.50) and a recommendation for setting an upper SpO<sub>2</sub> alarm limit are simple protocol refinements that may further improve adherence 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 adults with septic



shock employed a factorial design comparing an FiO<sub>2</sub> 1.0 with an SpO<sub>2</sub> target of 88–95% alongside hypertonic versus 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<sub>2</sub> 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<sub>x</sub>), 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 (O<sub>2</sub>-ICU) in the Netherlands, NCT02321072; Liberal Oxygenation Versus Conservative Oxygenation in ARDS (LOCO<sub>2</sub>) in France NCT02713451 and Targeted Oxygen therapy in Critical illness (TOXYC) NCT03287466 in the UK. Maitland and colleagues are conducting a large study of oxygen treatment thresholds combined with a comparison of high flow versus 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 control oxygen therapy prior to PICU

**Table 3 Clinical outcomes by treatment group**

Outcome	Conservative n = 54	Liberal n = 53	Effect estimates (95% CI)	p value
<b>Length of PICU stay from randomisation (days)</b>				
Median (IQR)	5 (4, 8)	6 (4, 11)	Median difference 1 (−0.8, 2.9)	0.292
<b>Length of invasive ventilation (days)</b>				
Median (IQR)	3 (2, 6)	3 (2, 6)	Median difference 0 (−1.64, 1.64)	1.0
<b>Ventilator-free days at day 30</b>				
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)		
<b>Days of cardiovascular support</b>				
Median (IQR)	0 (0,1)	0 (0,2)	Median difference 0 (−0.5, 0.5)	1.0
<b>Days of renal support</b>				
Median (IQR)	0 (0, 0)	0 (0, 0)	Median difference –	–
<b>Days receiving sedatives</b>				
Median (IQR)	3 (2,6)	4 (2,7)	Median difference 1 (−0.6, 2.6)	0.229
<b>PICU mortality</b>				
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

referral. 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<sub>2</sub> 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 versus liberal oxygenation in critically ill children. Considerations for a full trial include addition of an FiO<sub>2</sub> threshold for inclusion, and a recommendation for an upper SpO<sub>2</sub> alarm limit in the conservative group.

## Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-018-5232-7>) contains supplementary material, which is available to authorized users.

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## Compliance with ethical standards

## Conflicts of interest

No conflicts of interest to declare.

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