Longer-term survival, quality of life, and cost-effectiveness of conservative versus liberal oxygenation targets in critically ill children: a pre-specified analysis from Oxy-PICU, a multicentre, open, parallel-group, randomised controlled trial

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Summary

Background Peripheral oxygen saturation (SpO_2) above 94% is typical in children in paediatric intensive critical care units (PICUs) who are receiving invasive ventilation and supplemental oxygen. In a previous report from the Oxy-PICU trial, we showed that lower (conservative) oxygenation targets (SpO_2 88–92%) are beneficial, showing small but statistically significant differences in duration of organ support and large but non-significant cost reductions at 30 days. In this pre-specified analysis of the Oxy-PICU trial, we compare longer-term outcomes and cost-effectiveness of conservative versus liberal (SpO_2 >94%) oxygenation targets in children with emergency PICU admission.

Methods Oxy-PICU was a pragmatic, multicentre, open-label, randomised controlled trial in England and Scotland. Eligible children were older than 38 weeks and younger than 16 years and had been admitted for emergency care in one of 15 participating PICUs, where they received invasive respiratory support for abnormal gas exchange. Participants were randomly assigned (1:1) to either a conservative oxygenation target (SpO_2 88–92%) or liberal oxygenation target (SpO_2 >94%). Survival status was assessed at 90 days and 1 year, and health-related quality of life (HRQoL), quality-adjusted life-years (QALYs), health-care costs, and incremental net monetary benefit were assessed at 1 year after the index hospital admission and randomisation. HRQoL was measured with age-appropriate Paediatric Quality of Life Generic Core Scales and mapped onto the Child Health Utility 9D index score. HRQoL and survival data were combined to construct QALYs. Costs at 1 year were derived from use of hospital, outpatient, and community health services. The trial was registered in the ISRCTN registry (ISRCTN92103439).

Findings 2040 children were enrolled between Sept 1, 2020 and May 15, 2022. 1868 (91·6%) children were included in the 90-day survival analysis; of these 930 (49·8%) had been assigned liberal oxygen and 938 (50·2%) conservative oxygen. 1867 (91·5%) children were included in the 1-year survival analysis; 930 (49·8%) had been assigned liberal oxygenation and 937 (50·2%) conservative oxygen. At 90 days, 35 (3·7%) patients in the conservative oxygenation group and 45 (4·8%) patients in the liberal oxygenation group had died (adjusted hazard ratio [aHR] 0·75 [95% CI 0·48 to 1·17]). By 1 year, 52 (5·5%) patients in the conservative oxygenation group and 66 (7·1%) patients in the liberal oxygenation group had died (aHR 0·77 [95%CI 0·53 to 1·10]). Overall, mean HRQoL, life-years, and QALYs at 1 year were similar in the two groups. The adjusted incremental effect on cost of conservative oxygenation versus liberal oxygenation was –£879 (95% CI –9036 to 7278), whereas the incremental difference in QALYs was estimated at 0·001 (–0·010 to 0·011), leading to an incremental net monetary benefit of £894 (–7290 to 9078) associated with conservative oxygenation relative to liberal oxygenation. These results did not vary by age (<12 months *vs* ≥12 months), comorbidity at baseline, age-adjusted heart rate, or haemoglobin level at admission and were robust to alternative assumptions.

Interpretation Compared with usual care (SpO_2 >94%) for invasively ventilated children who are admitted as an emergency to a PICU, conservative oxygenation (SpO_2 88–92%) was not associated with differences in longer-term survival, costs, or cost-effectiveness. Taken together with previous findings of Oxy-PICU that conservative oxygenation compared with liberal oxygenation leads to better patient-centred and parent-centred outcomes at 30 days, these findings support the use of conservative oxygenation targets for this population.

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Research in context

Evidence before this study

The evidence before the Oxy-PICU trial was described along with the results of the primary clinical analysis. The primary analysis showed that among children admitted to emergency paediatric intensive care in the UK and who received invasive mechanical ventilation and supplemental oxygen with either a conservative target of peripheral oxygenation saturation (SpO_2 88–92%) or liberal target (SpO_2 >94%), conservative oxygenation provided a small but significant improvement in the duration of organ support and 30-day mortality. These findings suggested potential cost-effectiveness gains from conservative oxygenation, the analysis of which would hinge on longer-term survival data and hospital costs associated with conservative oxygenation therapy for critically ill children.

Added value of this study

Here we report the first results of the longer-term outcomes and cost-effectiveness of a conservative oxygenation target in critically ill children in the Oxy-PICU trial. We found no evidence of differences in 90-day or 1-year survival between patients who received conservative oxygenation and those who received liberal oxygenation during PICU care. Total costs did not differ between conservative oxygenation and liberal oxygenation strategies when use of health-care resources in hospital (both in the index admission and all subsequent readmissions), outpatient visits, and community health-care services up to 1 year were taken into account.

Implications of all the available evidence

Although conservative oxygenation for critically ill children who require invasive ventilation is beneficial in terms of short-term outcomes, the longer-term outcomes and cost-effectiveness remain uncertain. Given the benefit of conservative oxygenation on important patient-centred and parent-centred outcomes at 30 days, taken together, these longer-term outcomes and cost-effectiveness data support the choice of conservative oxygenation targets for critically ill children in need of respiratory support.

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See Online for appendix

Introduction

Critically ill children admitted to paediatric intensive critical care units (PICUs) often require invasive ventilation and supplemental oxygenation. Usual care for these patients is for high peripheral oxygen saturation (SpO_2 >94%).[1] Non-experimental evidence suggests that lower oxygenation targets might be superior for critically ill children with respiratory distress,[2–4] but there is little high-quality evidence from randomised controlled trials.[5]

The Oxy-PICU trial was the first large, randomised controlled trial comparing oxygen targets in critically ill children. The trial compared conservative (SpO_2 88–92%) versus liberal (SpO_2 >94%) oxygenation targets among 2040 children older than 38 weeks corrected gestational age and younger than 16 years who were admitted to PICU for emergency critical care and required invasive ventilation and supplemental oxygen. Small but significant benefits were associated with conservative oxygenation in terms of duration of organ support or mortality at 30 days when compared with the liberal oxygenation target.[6] Although improvements in short-term outcomes are important to both patients and clinicians, longer-term mortality and morbidity in terms of health-related quality of life are important patient-centred and parent-centred outcomes.

The finding that conservative oxygenation targets were associated with reduced duration of organ support might suggest that the strategy is also cost-effective because of shorter PICU stays and lower costs. In the primary analysis of the Oxy-PICU trial,[6] conservative oxygenation was associated with lower costs at 30 days. Although not statistically significant, the point estimate indicated an average saving of £2143 per patient with CIs strongly favouring conservative oxygenation, ranging from a cost saving of £4320 to an additional cost of £34. Although reductions in length of hospital stay, particularly in PICUs, provide the potential for more efficient use of scarce critical care beds, paediatric patients experiencing oxygen-related complications such as lung injury might require extended hospitalisation, additional treatments, and long-term rehabilitation. These costs can be substantial and affect health-care resources in the longer term and ultimately the cost-effectiveness of conservative oxygenation.

The aim of this prespecified analysis was to compare longer-term outcomes of conservative versus liberal oxygenation targets among children in critical care from the Oxy-PICU trial up to 1 year after index hospital admission and randomisation and to assess the cost-effectiveness of conservative and liberal oxygenation targets for children receiving invasive ventilation and supplemental oxygen during emergency hospital admissions.

Methods

Study design and participants

Oxy-PICU was a pragmatic, multicentre, open-label, parallel-group, randomised controlled trial in critically ill children, who were older than 38 weeks corrected gestational age and younger than 16 years, admitted to one of 15 participating PICUs as an emergency and receiving invasive respiratory support for abnormal gas exchange. Patients were randomly assigned (1:1) to either a conservative oxygenation target of SpO_2 88–92% or liberal oxygenation target of more than 94%, while receiving invasive respiratory support during their PICU stay. The protocol for the Oxy-PICU trial, including pre-specified statistical analysis plan and primary results from the trial, have been published elsewhere.[6,7] The aim of this study was to test the hypothesis that, among children

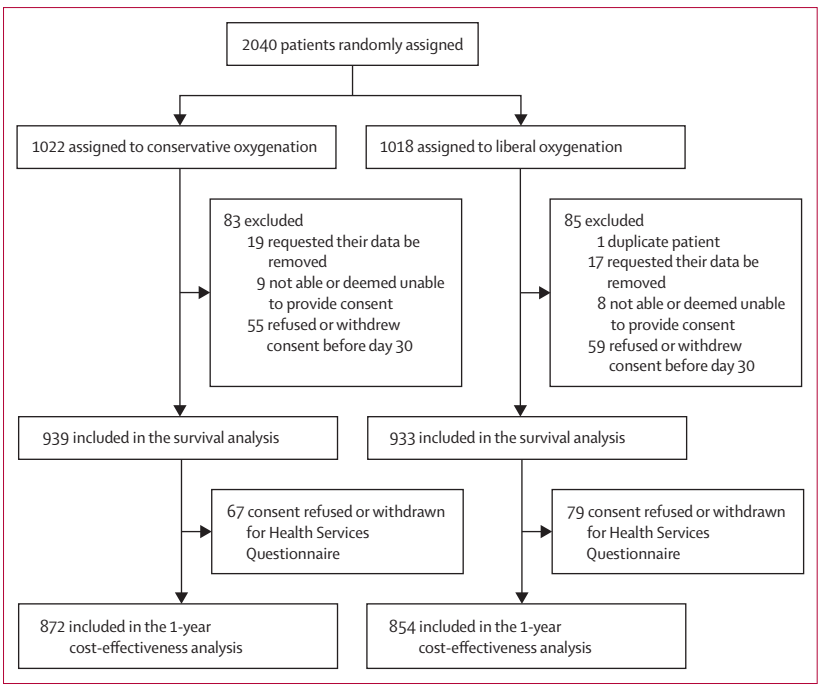

Figure 1: **Flow diagram for the longer-term survival and cost-effectiveness analyses of the Oxy-PICU trial**

admitted to PICU for emergency care and receiving invasive mechanical ventilation and supplemental oxygen, conservative oxygenation (SpO_2 88–92%) is associated with reduced mortality and is a cost-effective mode of treatment when compared to liberal oxygenation (SpO_2 >94%) at 90 days and at 1 year.

Because oxygenation targets are selected urgently, patients were enrolled following a research-without-prior-consent approach that received approval from a National Health Service (NHS) Research Ethics Committee (19/EE/0362). Written informed consent was sought from parents or legal guardians as soon as appropriate, typically within 24–48 h following randomisation. In the case of refusal or withdrawal of consent, data collected up to the point of refusal or withdrawal were retained unless the parents or legal guardians requested otherwise. At the point of consent for continuation in the trial, parents or guardians also provided consent and contact information for receipt of a follow-up health services questionnaire (HSQ) at 1 year following randomisation.

The trial was registered before commencement of recruitment with the ISRCTN registry (ISRCTN92103439).

Outcomes and data collection

Survival status at 90 days and 1 year, including date of death for non-surviving patients, was obtained by local investigators at participating hospitals using NHS Spine. We collated data collected through the trial patient case report form, information obtained via a bespoke HSQ and records from the Paediatric Intensive Care Audit Network (PICANet). The Oxy-PICU HSQ was developed as a part of the trial to assess outpatient and community health services and resource use at 1 year and was sent to all consented parents by post.

Health-related quality of life (HRQoL) information was obtained via age-appropriate Paediatric Quality of Life (PedsQL) Generic Core Scales, which were sent to all consented parents of surviving patients at 1 year.[8] The responses were mapped onto the Child Health Utility 9D (CHU-9D) index score[9] using an appropriate mapping function.[10] Quality-adjusted life-years (QALYs) at 1 year were calculated for each patient combining information on the patient's survival status and HRQoL at 1 year according to the area under the curve approach.[11] For decedents between randomisation and 1 year, we assumed a QALY of 0 for the 1-year period.[12] For survivors, we used linear interpolation between the baseline (assumed to be 0) and the 1-year CHU-9D score.

Key drivers of resource use were considered for calculating the total cost at 1 year of each intervention. We included care received in the PICU and general medical ward during the index hospital admission, all hospital readmissions up to 1 year, and use of outpatient and community health services following discharge from hospital up to 1 year.

PICU stays during the index admission and readmissions were costed according to the intensity of care received. Healthcare Resource Group (HRG) codes were derived for each day spent in the PICU applying the 2019/20 HRG4+ Grouper algorithm to information on the number of the patient's organs that required support.[13] The intensity of care required during stays in the general medical ward was assumed to be the same for all patients. No additional costs for delivering the interventions were included. The duration of the PICU stay was extracted from PICANet and the duration of general medical ward stay from the case report form.

We sourced information about PICU readmissions following discharge from index hospital admission from the PICANet. We extracted further information on inpatient stays as well as hospital outpatient visits and community services following discharge from the index hospital admission up to 1 year from randomisation from the HSQ. Due to the right-skewness of the self-reported readmissions length data, we decided to assume a maximum total duration of readmissions of 50 days for patients reporting total durations greater than 50 days (95% of patients who completed the questionnaire reported a total readmissions duration shorter than 50 days). Two alternative values for this assumption were considered in sensitivity analyses. Total costs were calculated by combining the resource use with unit costs at 2020–21 prices (appendix p 4). Unit cost data were extracted from the 2021 NHS Reference Cost collection and the 2021 Personal Social Services Research Unit report of Health and Social Care costs.[14]

The primary economic outcome was the incremental net monetary benefit (INB) at 1 year of conservative oxygenation versus liberal oxygenation during critical care in hospital. The INB was calculated valuing estimated incremental QALYs by the willingness-to-pay threshold recommended by the National Institute for Health and Care Excellence of £20 000 per QALY gained, and then subtracting the incremental costs.[15] We have included a completed CHEERS 2022 checklist in the appendix (p 7–10).[16]

Statistical analysis

The Oxy-PICU sample size was based on the outcomes observed during the Oxy-PICU pilot trial.[17] 2040 patients were required for the primary clinical-effectiveness analyses (reported elsewhere[17]) to provide 90% power to detect a 12-h reduction in the mean duration of organ support from 120 h to 108 h (based on the data observed in the pilot trial), with a significance threshold of $p<0\cdot05$.[6]

Survival status at 90 days and 1 year was assessed in the intention-to-treat population, defined as all patients who were randomly assigned to either liberal or conservative oxygenation except for those who did not provide or withdrew consent before 30 days. Patients who refused or withdrew consent after 30 days were included in the 90-day and 1-year survival analyses, but censored at the point of withdrawal or loss to follow-up. HRQoL, life-years, QALYs, costs, and INB in the cost-effectiveness analysis were analysed by ITT in the subset of all patients who consented to receiving the HSQ at 1 year (ITTc population).

90-day and 1-year survival were compared between the liberal and conservative oxygenation groups by Kaplan–Meier analysis, with patients censored at last available follow-up and using Cox regression to calculate hazard ratios (HRs) and 95% CIs with adjustment for baseline covariates age (<12 months *vs* ≥12 months), primary reason for admission (lower respiratory tract infection *vs* other), severity of abnormality of gas exchange (SpO_2 to fraction of inspired oxygen ratio <221 with positive end-expiratory pressure ≥5 *vs* other), and predicted mortality at time of PICU admission (measured using the Paediatric Index of Mortality 3 [PIM3] score[18]). Due to the low event rate, the Kaplan–Meier plot is presented as cumulative mortality, not survival. The proportional hazards assumption was tested using the Schoenfeld residuals, and the linear relationship with the PIM3 covariate was assessed graphically using the Martingale residuals.

The cost-effectiveness analysis adopted an NHS and Personal Social Services perspective, and the results were reported as both adjusted (as per survival analysis) and unadjusted mean differences (95% CI) between the liberal and conservative oxygenation groups in HRQoL, life-years, QALYs, and costs at 1 year. We used the seemingly unrelated regressions (SUR) method to estimate incremental costs and QALYs, which were

	Conservative oxygenation (n=872)	Liberal oxygenation (n=854)
Age, years		
At time of admission	2·6 (4·1)	2·5 (3·9)
Missing	0	0
Aged <12 months		
At time of admission	419 (48·1%)	400 (46·8%)
Missing	0	0
Sex		
Female	372 (43·0%)	383 (45·3%)
Male	493 (57·0%)	462 (54·7%)
Missing	7 (0·8%)	9 (1·1%)
Ethnic background (grouped)		
White	515 (59·1%)	494 (57·8%)
Asian	86 (9·9%)	89 (10·4%)
Black	49 (5·6%)	51 (6·0%)
Mixed	33 (3·8%)	37 (4·3%)
Other	28 (3·2%)	38 (4·4%)
Missing	161 (18·5%)	145 (17·0%)
Reason for PICU admission		
Lower respiratory tract infection	563 (64·6%)	559 (65·5%)
Other	309 (35·4%)	295 (34·5%)
Missing	0	0
Severity of gas exchange		
SpO_2:FiO_2 ratio <221 (with positive end-expiratory pressure ≥5)	515 (59·1%)	509 (59·6%)
Other	357 (40·9%)	345 (40·4%)
Missing	0	0
Predicted mortality (PIM3)		
At time of admission	3·7% (6·2)	3·9% (6·5)
Missing	0	0
At least one comorbidity		
No	449 (51·5%)	404 (47·5%)
Yes	423 (48·5%)	447 (52·5%)
Missing	0	3 (0·4%)
Age-adjusted heart rate		
<10th percentile	67 (7·9%)	69 (8·3%)
10th to <50th percentile	190 (22·4%)	198 (23·7%)
50th to <90th percentile	334 (39·3%)	328 (39·3%)
90th to <95th percentile	83 (9·8%)	74 (8·9%)
95th to <99th percentile	113 (13·3%)	104 (12·5%)
≥99th percentile	63 (7·4%)	61 (7·3%)
Missing	22 (2·6%)	20 (2·4%)
Haemoglobin, g/L		
At time of admission	103·2 (17·9)	103·8 (20·3)
Missing	258 (29·6%)	222 (26·0%)

Data are n (%) or mean (SD). Results are reported for the population of patients in the intention-to-treat population who consented to receive the health service questionnaire at 1 year after their index hospital admission, following multiple imputation to handle missing data. "Missing" shows the number of patients (n [%]) for whom data was not available. FiO_2=fraction of inspired oxygen. SpO_2=peripheral oxygenation saturation. PIM3=Paediatric Index of Mortality 3.

Table 1: **Baseline characteristics of population included in the cost-effectiveness analysis of the Oxy-PICU trial**

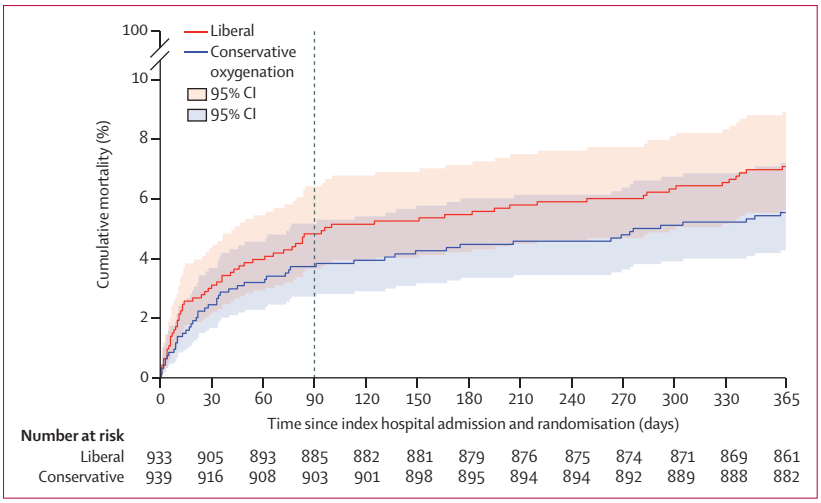

Figure 2: **Kaplan–Meier plot of mortality among patients receiving conservative oxygenation or liberal oxygenation therapy**

The analysis included those patients in the intention-to-treat population who consented to receiving a Health Services Questionnaire at 1 year after the index hospital admission and randomisation, requesting data pertaining to survival status before each respective timepoint. Dashed line marks the 90-day time point.

	Conservative oxygenation (n=872)	Liberal oxygenation (n=854)
Mortality	47 (5·4%)	50 (5·9%)
CHU-9D index score of 1-year survivors	0·913 (0·047)	0·915 (0·048)
Life-years	0·946 (0·226)	0·941 (0·235)
QALYs	0·432 (0·106)	0·431 (0·110)

Data are n (%) or mean (SD). Results are reported for the population of patients in the intention-to-treat population who consented to receive the health service questionnaire at 1 year after their index hospital admission, following multiple imputation to handle missing data. CHU-9D=Child Health Utility 9 Dimension. QALYs=quality-adjusted life-years.

Table 2: **1-year mortality, CHU-9D score, life-years, and QALYs**

subsequently used to calculate the INB.[19] A single-level SUR model was used in the base-case analysis because of the low site-level variances in costs and QALYs. Models were adjusted for baseline covariates.

Missing data were addressed with multivariable imputation by chained equations (MICE), assuming data were missing at random conditional on baseline covariates, resource use, and observed endpoints (which included 1-year mortality).[20] Resultant estimates were combined with Rubin's rules to recognise uncertainty both within and between imputations.[21] A cost-effectiveness plane was used to show the uncertainty in costs and QALY estimates associated with conservative and liberal oxygenation, which were obtained by randomly generating 800 draws from the joint distribution of these two endpoints, assuming asymptotic normality.

We assessed cost-effectiveness in prespecified subgroups defined by age (<12 months *vs* ≥12 months), comorbidity at baseline (defined as a pre-existing condition present within 12 months of PICU admission), age-adjusted heart rate (<10th percentile, 10th to <50th percentile, 50th to <90th percentile, 90th to <95th percentile, 95th to <99th percentile, and ≥99th percentile), and haemoglobin level at admission.

In sensitivity analyses, we assessed the following base case assumptions: (1) a multilevel regression model to allow for clustering of patients at sites, rather than a single-level regression model; (2) a gamma model (with identity link) for costs and QALYs, instead of a normal distribution; (3) a 10% increase in all unit costs; (4) a 10% decrease in all unit costs; (5) an alternative algorithm for mapping the PedsQL score to the CHU-9D index from an Australian population,[22] rather than a UK population; and (6) alternative assumptions about the maximum total readmission duration (40 days and 60 days).

90-day and 1-year survival were analysed with "Survival-time data" commands in Stata (version 17). Stata's mi suite of commands was used for multiple imputation. The *sureg* estimation command was used for jointly estimating costs and QALYs.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Oxy-PICU enrolled 2040 critically ill children between Sept 1, 2020, and May 15, 2022, who were admitted to PICU for ventilation support. Baseline patient characteristics have been reported.[6] 1872 (91·8%) children were included in the survival analysis (of whom 933 [49·8%] had been assigned liberal oxygen and 939 [50·2%] conservative oxygen). Five children were censored at the time of withdrawal after day 30 (one in the liberal oxygen group and one in the conservative oxygen group) or at last recorded follow-up (two in the liberal oxygen group before day 90 and one in the conservative oxygen group after day 90). Reasons for excluding 85 (8·3%) of 1018 randomly assigned children in the liberal oxygen group and 83 (8·1%) of 1022 randomly assigned children from the conservative oxygen group are listed in figure 1. 1726 (84·6%) patients consented to receive the HSQ and were included in the cost-effectiveness analysis (this ITTc population included 854 children in the liberal oxygen group and 872 children in the conservative oxygen group). The characteristics of patients who consented to receiving the HSQ and who were included in the ITTc population are shown in table 1 and are representative of the overall cohort.

At 90 days, 35 (3·7%; 95% CI 2·7–5·2) patients in the conservative oxygenation group and 45 (4·8%; 3·6–6·4) patients in the liberal oxygenation group had died (adjusted hazard ratio 0·75 [95% CI 0·48–1·17]). Deaths

increased in both groups at 1 year following randomisation to 52 (5·5%; 4·3–7·2) patients in the conservative oxygenation group and 66 (7·1%; 5·6–8·9) patients in the liberal oxygenation group (0·77 [0·53–1·10]; intention-to-treat analysis). The Kaplan–Meier analysis of cumulative mortality revealed wide estimate uncertainty and no difference in overall survival with conservative versus liberal oxygenation (figure 2).

Responses to the HSQ were obtained for 1038 (60·1%) of 1726 patients. Baseline characteristics for HSQ responders are reported in the appendix (p 5). Overall, mean HRQoL, life-years, and QALYs at 1 year were similar in the two groups (table 2). Of the four PedsQL domains, among patients who were alive at the end of the 1 year after initial hospital admission, the lowest scores were in the emotional domain, and the highest in the social domain (appendix p 6).

The mean total duration of hospital stay during the index admission and subsequent readmissions, including all time spent in the PICU is compared in table 3. By 1 year, the mean duration of stay in hospital was similar among patients in the liberal oxygenation group and conservative oxygenation group (24·90 days (SD 36·24) *vs* 25·04 days [41·28]).

Total costs, including those accrued during the index hospital admission and all subsequent readmissions, as well as those costs derived from use of outpatient and community health-care services up to 1 year are compared in table 3. In both groups, the cost of index hospital stays accounted for most of the total costs, and the cost of PICU stays was the main driver of total index hospital stay costs (table 3). Outpatient, primary and community care services, and readmissions into hospital accounted for a small fraction of costs in both groups (table 3).

The adjusted mean differences in costs at 1 year are shown in table 4. The adjusted INB obtained by jointly modelling costs and QALYs was £894 (–7290 to 9078; table 4). The incremental results presented in the cost-effectiveness plane were evenly distributed (figure 3). In subgroup analyses, cost-effectiveness results varied little across pre-specified population subgroups (appendix p 11). The base-case results were robust to alternative scenarios considered in sensitivity analyses (appendix p 12).

	Conservative oxygenation (n=872)	Liberal oxygenation (n= 854)
Resource use		
Index hospital admission		
Total duration of stay in hospital, days	17·5 (36·4)	18·6 (33·9)
Duration of stay in PICU, days	7·8 (12·2)	8·5 (13·6)
Duration of stay in general medical ward, days	9·7 (31·7)	10·1 (26·3)
Readmission		
Number of patients with at least one readmission	481 (55·1%)	477 (55·8%)
Duration of stay in hospital, days*	7·5 (14·7)	6·3 (10·5)
Duration of stay in PICU, days	1·8 (10·8)	1·4 (7·0)
Duration of stay in general medical ward*	5·7 (8·9)	4·9 (6·8)
Total duration of stay by 1 year post index admission, days*	25·04 (41·28)	24·90 (36·24)
Costs		
Index hospital admission		
Cost of index hospital admission, £*	44 642 (72 805)	48 567 (76 827)
Cost of stay in PICU, £	27 803 (36 019)	31 074 (47 215)
Cost of stay in general medical ward, £	16 839 (54 864)	17 493 (45 522)
Readmission		
Cost of readmission, £*	15 870 (41 057)	13 167 (27 004)
Cost of stay in PICU, £	6008 (36 387)	4611 (22 563)
Cost of stay in general medical ward, £*	9862 (15 324)	8556 (11 828)
Cost of outpatient, primary, and community care services, £*	1645 (1406)	1892 (1805)
Total cost 1 year after index admission, £*	62 156 (89 037)	63 627 (83 102)

Data are n (%) or mean (SD). PICU=paediatric intensive care unit. *Results are reported for the population of patients in the intention-to-treat population who consented to receive the health service questionnaire at 1 year after their index hospital admission, following multiple imputation to handle missing data.

Table 3: **Use of health resources and costs in index admission and all subsequent readmissions up to 1 year**

	Incremental effect (unadjusted mean difference [95% CI])	Incremental effect (adjusted mean difference [95% CI])*
Total cost, £	–1470 (–9804 to 6863)	–879 (–9036 to 7278)
CHU-9D index score	–0·002 (–0·010 to 0·009)	–0·001 (–0·010 to 0·008)
Life-years	0·005 (–0·017 to 0·026)	0·003 (–0·018 to 0·024)
QALYs	0·001 (–0·009 to 0·012)	0·001 (–0·010 to 0·011)
Incremental net monetary benefit, £	1500 (–6869 to 9869)	894 (–7290 to 9078)

Results are reported for the population of patients in the intention-to-treat population who consented to receive the health service questionnaire at 1 year after their index hospital admission, following multiple imputation to handle missing data. The incremental net monetary benefit was calculated according to National Institute for Health and Care Excellence methods guidance, by multiplying the mean QALY gain (or loss) by £20 000, and subtracting from this the incremental cost. CHU-9D=Child Health Utility 9 Dimension. QALYs=quality-adjusted life-years. *The incremental effects are reported after applying case-mix adjustment.

Table 4: **Cost-effectiveness of conservative oxygenation relative to liberal oxygenation at 1 year**

Discussion

In this analysis of the longer-term outcomes of the Oxy-PICU trial and cost-effectiveness of conservative versus liberal oxygenation targets in critically ill children, we found no statistically significant differences in 90 days and 1-year mortality between patients in the conservative and liberal oxygenation groups, with wide uncertainty surrounding the estimates. We did not find any statistically significant differences in costs and QALYs at 1 year, and we observed an INB point estimate of £894 favouring conservative oxygenation (95% CI –£7290 to £9078). The main driver of costs at 1 year was the index hospital admission, accounting for around 70% of the total cost. Of these costs, the cost of PICU care was the largest cost item. In general, results were similar across pre-specified population subgroups and fairly robust to key assumptions made in the base case (appendix pp 11, 12).

These results complement those of the primary clinical research paper,[6] which showed that a conservative oxygenation target is associated with a small but

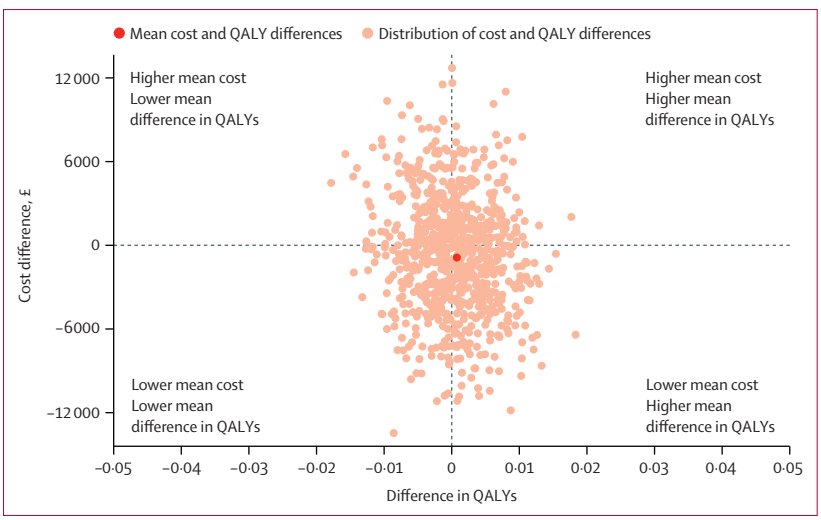

***Figure 3*: Cost-effectiveness plane of the incremental costs and QALYs associated with conservative oxygenation relative to liberal oxygenation therapy**

Results are reported for the population of patients in the intention-to-treat population for whom consent to receive the health service questionnaire at 1 year was provided, following multiple imputation to handle missing data. QALY=quality-adjusted life-year.

significant reduction in the duration of organ support or death at 30 days compared with the liberal oxygenation target. Across both the primary paper and the present analyses, survival at each timepoint was higher in the conservative oxygenation group than in the liberal oxygenation group, but there is wide uncertainty around the estimates.

The finding that conservative oxygenation therapy is not associated with differences in costs or cost-effectiveness at 1 year follow-up, with wide uncertainty surrounding the estimates, complement those in the primary report.[6] Although not statistically significant, a conservative oxygenation target was associated with reduced costs at 30 days, with the uncertainty estimates both strongly favouring conservative oxygenation. This cost-effectiveness analysis considered the same pre-specified subgroups as in the primary analysis of clinical effectiveness[6] and showed consistency between subgroup cost-effectiveness and the primary clinical outcome (duration of organ support). In both cases, no heterogeneity patterns were observed across the pre-specified population subgroups. Importantly, however, the study was not designed to detect a subgroup effect for either clinical effectiveness or cost-effectiveness endpoints and, hence, the subgroup results should be viewed as exploratory.

Although previous studies had investigated the effects of different oxygenation targets in paediatric populations on different resource-use dimensions, this is the first study, to our knowledge, to assess outcomes in patients admitted to PICU and to include a full cost-effectiveness analysis. Previously, Cunningham and colleagues[23] investigated the effect of SpO_2 thresholds (90% *vs* 94%) in infants older than 6 weeks and 12 months or younger admitted to general paediatric wards with bronchiolitis. The study found that the 90% target could be a cost-effective mode of treatment, associated with reduced costs and improved outcome (days to cough resolution), when compared with the standard of care of a 94% threshold. In line with our findings, Cunningham and colleagues also found that patients in the lower threshold group were discharged earlier (10-h difference *vs* 24-h difference in our study). Similar results were observed in one other study[24] comparing an 80% threshold in children younger than 12 years with pneumonia and hypoxaemia in east Africa with a 92% threshold (15-h difference). One observational study[25] found that patients aged 6 weeks to 12 months with bronchiolitis who were admitted into paediatric departments in the UK with oxygen saturation thresholds for admission of 90% were discharged earlier than those admitted to centres with 92% thresholds (18-h difference). Some previous studies had also investigated the effects of oxygenation targets on readmission rates, which is another driver of total costs. In line with our findings, neither Cunningham and colleagues[23] nor Schuh and colleagues[26] found statistically significant differences in readmission rates. However, the unadjusted comparison of mean length of stay in readmissions in our study reveals that patients in the conservative target oxygenation group could have slightly longer readmission stays than those in the liberal oxygenation group.

This study has several strengths. It is, to the best of our knowledge, the only study to date to report longer-term outcomes associated with conservative oxygenation with a high follow-up rate for survival outcomes (around 92%) at 90-day and 1-year timepoints. We used a prospectively designed economic evaluation integrated within a large, multicentre, randomised controlled trial. We collected detailed data on resource use and health economic outcomes for each randomly assigned patient using multiple linked databases. Hospital resource-use data were collected using the trial case report form and then linked to information about intensity of care received in the PICU from the PICANet national clinical audit, as well as information on health-service use through linkage to follow-up HSQs. Information on HRQoL was measured with age-appropriate versions of the widely used PedsQL Generic Core Scales. These scores were mapped to the CHU-9D score using validated mapping algorithms to construct QALYs for each patient. Missing data for the resource-use items and HRQoL collected through the HSQ were handled using the recommended MICE approach.[20,21] Notably, the economic analysis adhered to a harmonised and pre-specified statistical and economic analysis plan, ensuring the highest standards of methodological design and a consistent approach for an analysis of clinical and health-economic endpoints. Comprehensive sensitivity analyses were carried out, and the base-case results were not sensitive to alternative assumptions.

The limitations of the Oxy-PICU trial have been discussed.[6] Regarding the present analyses, the pre-specified secondary outcomes of survival at 90 days and 1 year were not sufficiently powered to detect significant differences between the two groups, which is reflected in the wide uncertainty observed in these outcomes. Moreover, as a pragmatic trial with a large number of patients, we were unable to collect information relating to the cause of death, which precludes the possibility of further analyses that might explain the numerical differences observed in these outcomes. The cost-effectiveness analysis used data from an HSQ. Differences between responders and the overall population might not have been fully accounted for in the analysis and could potentially lead to bias. Also, HRQoL was measured using a generic questionnaire, which might not be sufficiently sensitive to capture changes that are relevant for these patients. The cost-effectiveness analysis using the well-designed, large, multicentre Oxy-PICU study has high internal validity for supporting decision making in the UK NHS. However, the cost-effectiveness results of this study are less likely to be generalisable to other decision-making contexts that have different cost structures.

In conclusion, this study shows that there is considerable statistical uncertainty in the longer-term survival and cost-effectiveness of a conservative oxygenation target of SpO_2 88–92% compared with a usual-care liberal oxygenation target of SpO_2 greater than 94% for critically ill children receiving invasive ventilation and supplemental oxygenation. Given the previously reported benefit of conservative oxygenation on important patient-centred and parent-centred outcomes at 30 days, when taken together, the findings support the use of a conservative oxygenation target for critically ill children receiving invasive mechanical ventilation.

Contributors

MJP, SR, RA, ED, LE-M, JP, PR, KT, KMR, DAH, PRM, and ZS conceptualised Oxy-PICU and were involved in funding acquisition. All authors oversaw trial conduct and management, and contributed to acquisition, analysis, and interpretation of the data. SM-Z, ZS, DWG, and EG directly accessed and verified the data and conducted the analyses. SM-Z, MJP, DWG, and ZS wrote the original draft paper, which all authors commented on. All authors critically revised and approved the manuscript for submission.

Declaration of interests

SR and MP report funding to their institution from the UK Engineering and Physical Science Research Council and SR reports consulting fees, honoraria, and travel fees from La Roche and the Malaysian Society of Intensive Care during the study period. KR is Director of the National Institute for Health and Social Care Research (NIHR) Health and Social Care Delivery Research Programme.

Data sharing

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data for scientific research may be granted following review.

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