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Protocol for a Randomized Multiple Center Trial of Conservative Versus Liberal Oxygenation Targets in Critically Ill Children (Oxy-PICU): Oxygen in Paediatric Intensive Care

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OBJECTIVES: Oxygen administration is a fundamental part of pediatric critical care, with supplemental oxygen offered to nearly every acutely unwell child. However, optimal targets for systemic oxygenation are unknown. Oxy-PICU aims to evaluate the clinical effectiveness and cost-effectiveness of a conservative peripheral oxygen saturation (Spo_2) target of 88–92% compared with a liberal target of more than 94%.

DESIGN: Pragmatic, open, multiple-center, parallel group randomized control trial with integrated economic evaluation.

SETTING: Fifteen PICUs across England, Wales, and Scotland.

PATIENTS: Infants and children age more than 38 week-corrected gestational age to 16 years who are accepted to a participating PICU as an unplanned admission and receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange.

INTERVENTION: Adjustment of ventilation and inspired oxygen settings to achieve an Spo_2 target of 88–92% during invasive mechanical ventilation.

MEASUREMENTS AND MAIN RESULTS: Randomization is 1:1 to a liberal Spo_2 target of more than 94% or a conservative Spo_2 target of 88–92% (inclusive), using minimization with a random component. Minimization will be performed on: age, site, primary reason for admission, and severity of abnormality of gas exchange. Due to the emergency nature of the treatment, approaching patients for written informed consent will be deferred to after randomization. The primary clinical outcome is a composite of death and days of organ support at 30 days. Baseline demographics and clinical status will be recorded as well as daily measures of oxygenation and organ support, and discharge outcomes. This trial received Health Research Authority approval on December 23, 2019 (reference: 272768), including a favorable ethical opinion from the East of England–Cambridge South Research Ethics Committee (reference number: 19/EE/0362). Trial findings will be disseminated in national and international conferences and peer-reviewed journals.

KEY WORDS: child; critical care; hyperoxia; hypoxia; mechanical ventilation; oxygen saturation

Supplemental oxygen is offered to nearly every acutely unwell child. Each year in the United Kingdom, around 11,000 of the most seriously ill children are referred to intensive care as an emergency, of whom at least 7,500 receive both invasive mechanical ventilation and supplemental oxygen (1).

However, the optimal targets for systemic oxygenation are unknown. Practice varies with age, diagnosis, and treating clinician (2, 3). Other than in the subset

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of cases with congenital heart disease, current practice is to administer supplemental oxygen to achieve peripheral oxygen saturation (Spo_2) at, or above, the normal healthy range (4). Observational data suggest harm from too generous use of supplemental oxygen in adults (5) and children (6). Lower thresholds for commencing supplemental oxygen have been shown to be equivalent to standard care in randomized controlled trials (RCTs) among ward admissions of infants with acute bronchiolitis in the United Kingdom and children with severe pneumonia in Uganda (7) and Kenya (8).

Currently, there is no RCT evidence to guide pediatric intensive care staff on the most effective way to use supplemental oxygen in critically ill children. The Oxygen in Paediatric Intensive Care (Oxy-PICU) trial is attempting to reduce this uncertainty. We previously successfully completed a pilot trial, which demonstrated the feasibility of a large pragmatic RCT comparing conservative and liberal oxygenation targets in a pediatric setting, and informed the design and conduct of this trial.

MATERIALS AND METHODS

Aim

To determine if the risks of interventions employed to raise Spo_2 to more than 94% exceed their benefits when compared with an Spo_2 of 88–92%.

Primary Objective

To evaluate the clinical and cost-effectiveness of a conservative Spo_2 target (88–92%) on a composite outcome of mortality and duration of organ support at 30 days (rank-based analysis with death ranked as worse than 30 d of organ support).

Design and Setting

Oxy-PICU is a pragmatic, open, multiple-center, parallel group RCT with integrated economic evaluation in infants and children accepted for unplanned admission to 15 National Health Service (NHS) PICUs across England, Wales, and Scotland and their regional retrieval services.

Screening and Randomization

Potentially eligible infants and children admitted/accepted for admission to the participating PICU will be screened against the inclusion/exclusion criteria by the local clinical or transport team (**Table 1** and **Fig. 1**). Patients will be randomized on a 1:1 basis to either a liberal (>94%) or a conservative (88–92%) Spo_2 target using a computer-generated dynamic procedure (minimization) with a random component. Each participant will be allocated with 80% probability to the group that minimizes the between-group differences in these factors among all participants recruited to the trial to date and to the alternative group with 20% probability.

Prerandomization and Postrandomization Care

Prior to randomization, all care will be determined by the clinical team primarily responsible for the child's treatment and care. Following randomization, the randomized treatment will be commenced as soon as practically possible. This means adjustment of ventilator and inspired oxygen to: the lowest settings/concentrations with the intention of achieving between 88% and 92% where possible during invasive mechanical ventilation for those randomized to the conservative Spo_2 target, and the settings required to maintain Spo_2 above 94% for those randomized to the liberal target.

The choice of settings to achieve the Spo_2 target and all other care is at the discretion of the clinical team.

Consent Procedures

Children eligible for Oxy-PICU will most often need oxygen treatment started in a life-threatening emergency, where any delay in commencing treatment could be detrimental. In order to minimize additional distress/burden on families during this time, Oxy-PICU will use a deferred consent (or "research without prior consent") model, whereby a detailed consent discussion will occur after randomization. This model was developed in line with the CONseNt methods in pediatric Emergency and urgent Care Trials (CONNECT) guidance (9) and has been found to be acceptable to both parents/guardians and clinicians in the PICU setting (10–12), and parents in the Oxy-PICU pilot (13).

Once a patient is identified as being eligible for the trial, they will be randomized and the randomly assigned treatment commenced as soon as possible. Following randomization, a trained, delegated member of the site research team will approach the parents/legal guardians as soon as practically and appropriately possible (usually within 24–48 hr of randomization) to

TABLE 1.
Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Aged <16 yr and >38 wk corrected gestational age	Death perceived as imminent
Enrolled within 6 hr of first meeting all the following criteria	Brain pathology/injury as primary reason for admission (e.g., traumatic brain injury, postcardiac arrest, stroke, and convulsive status epilepticus without aspiration)
Accepted to a participating PICU as an unplanned admission	Known pulmonary hypertension
Receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange	Known or suspected sickle cell disease
Face-to-face contact with PICU staff or transport team	Known or suspected uncorrected congenital cardiac disease
	End-of-life care plan in place with limitation of resuscitation
	Receiving long-term invasive mechanical ventilation prior to this admission
	Recruited to Oxy-PICU in a previous admission

discuss the trial and provide a participant information sheet detailing the purpose of the trial; what participation involves; confidentiality and use of data; and availability of trial results. A Consent Form will also be provided indicating that: the information given has been read and understood; consent is given for continuation in the trial, access to medical records for data collection, receipt of follow-up questionnaires, and for anonymized data to be shared in future.

A modification of the consent procedure will be utilized for two situations where either the patient: 1) is discharged from hospital prior to obtaining consent or 2) dies prior to consent being sought. In the former, the local research team will contact the parent/guardian, initially by phone and then by post, for consent. If there is no response after 4 weeks, postal contact will be made again. If no consent form is received within 4 weeks of the second letter, the participant will be included in the trial unless they notify the research team otherwise. In the latter situation, the local research team will consult with colleagues and bereavement counselors to establish the most appropriate clinical/research team member and time to notify the parents/guardians of involvement in the trial. If approach for consent prior to their departure from hospital is deemed not appropriate, then they will be approached by post 4-week postrandomization. If there is no response after 4 weeks, postal contact will be made again. If no consent form is received within 4 weeks of the second letter, the participant's data will be included in the trial.

Safety Monitoring

Adverse event (AE) reporting will follow the Health Research Authority guidelines on safety reporting in studies, which do not use Investigational Medicinal Products.

The following events have been prespecified as potential AEs that could be related to trial Spo_2 target and observed in participants from the time of randomization until 30 days after randomization or discharge from PICU, whichever is later: new onset of severe lactic acidosis (>5 mmol/L) without otherwise known cause, new onset of cardiac ischemia without otherwise known cause, new onset of acute kidney injury without otherwise known cause, and new onset of seizures without otherwise known cause.

Occurrences of the specified, expected AEs will be recorded for all randomized patients. Considering that all infants and children eligible for Oxy-PICU are critically ill and at increased risk of experiencing AEs due to the complexity of their condition, occurrences of nonspecified AEs will only be reported if considered to be related to trial Spo_2 target (i.e., "possibly," "probably," or "definitely"). Any event classified as "severe" or "life-threatening" in severity is considered a serious adverse event (SAE) and must be reported to the Intensive Care National Audit & Research Centre (ICNARC) Clinical Trials Unit (CTU). If the SAE is evaluated by the Trial Management Group (TMG) as a related and unexpected SAE, the ICNARC CTU will submit a report to the Research Ethics Committee (REC) within 15 calendar days.

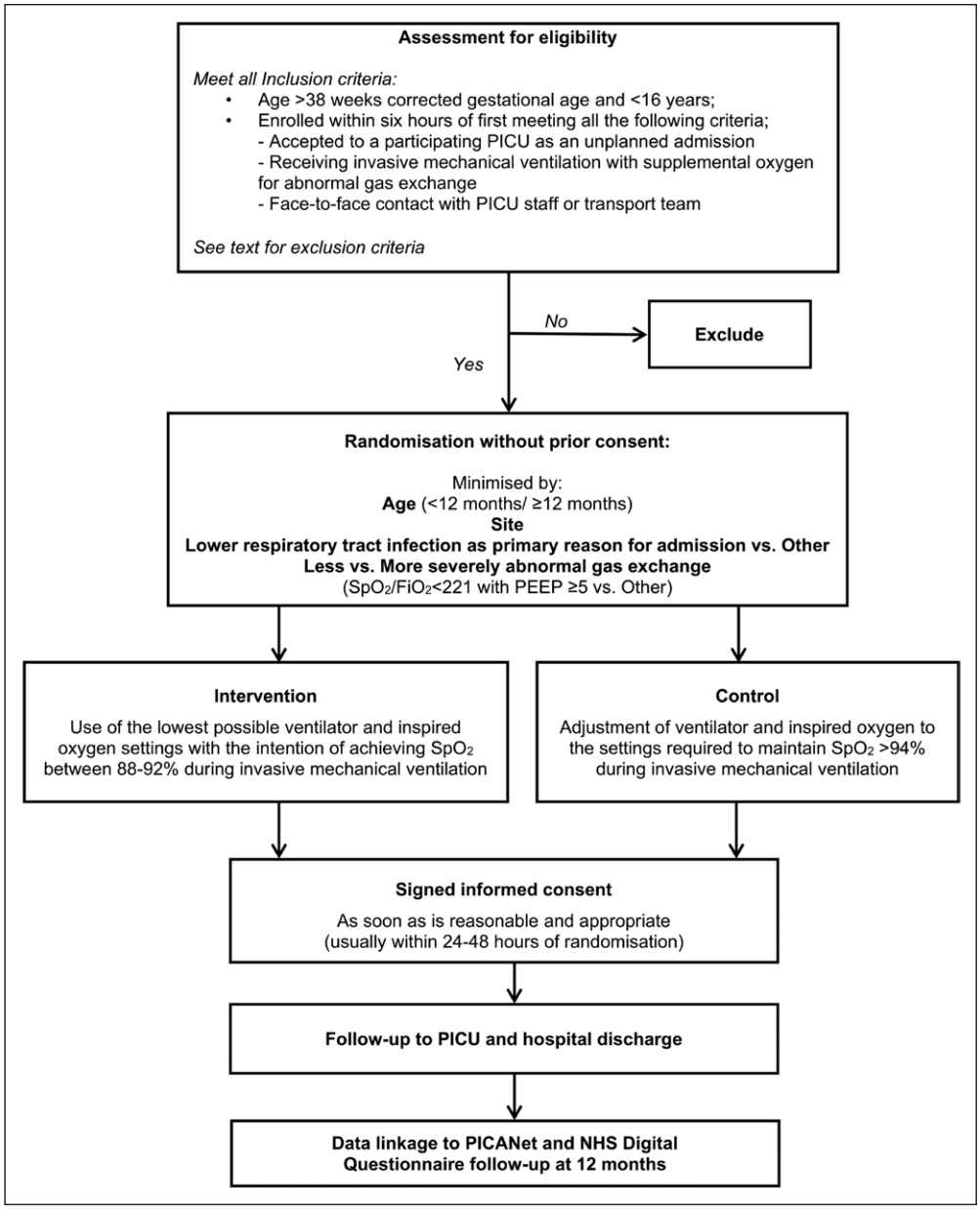

Figure 1. Trial schema of eligibility, randomization, and intervention to discharge and follow-up. NHS = National Health Service, PEEP = positive end-expiratory pressure, PICANet = Pediatric Intensive Care Audit Network, Spo_2 = peripheral oxygen saturation.

Questionnaire Follow-Up

Each participant will be followed up at 12 months post-randomization to assess health-related quality of life (HrQoL). After ascertaining survival status, ICNARC CTU will send a questionnaire containing the Pediatric Quality of Life Inventory (PedsQL) and the Child Heath Utility 9D (CHU-9D) to the parents/guardians of recruited patients via e-mail or post as per their preference indicated at the time of consent. If there is no response within 3 weeks, parents/guardians will be followed up by telephone.

Approvals

The trial received Health Research Authority approval (Integrated Research Application System number: 272768) on December 23, 2019, including a favorable ethical opinion from the East of England—Cambridge South REC (reference number: 19/EE/0362).

OUTCOME MEASURES

Primary Outcome

The primary clinical effectiveness outcome is a composite of mortality and duration of organ support, defined by the Pediatric Critical Care Minimum Dataset (PCCMDS) (14), at 30 days. A full list of trial outcomes can be found in **Table 2**.

Data Collection

Trial-specific data collection is limited to the minimum required to deliver trial objectives and will be collected at baseline prior to randomization, daily, at discharge from PICU, and 30 days, 90 days, and 12 months following randomization (**Table 3**). Oxy-PICU works closely with the Pediatric Intensive Care Audit Network (PICANet) to make best use of established PICU registry data. Recruited patients will be asked for their consent for data linkage with routine sources (e.g., national death registration data via NHS Digital or equivalent). Participant data will be entered onto the secure electronic case report form database and will undergo validation checks. Any incomplete, inaccurate, or inconsistent data will be queried with the research team at participating sites for resolution.

TABLE 2.
Trial Outcome Measures

Outcomes	Clinical Effectiveness	Cost-Effectiveness
Primary	Composite of mortality and duration of organ support, defined by the Pediatric Critical Care Minimum Dataset (14), at 30 d	
Secondary	Mortality at PICU discharge, 30 d, 90 d, and 12 mo Liberation from ventilation Duration of organ support Functional status at PICU discharge and at 12 mo, measured by the Pediatric Overall Performance Category and Pediatric Cerebral Performance Category scales Length of PICU and hospital stay Health-related Quality of Life at 12 mo, measured by the child, self-, or parent-proxy reported Pediatric Quality of Life Inventory (15) and Child Health Utility-9D questionnaire (16)	Incremental costs, quality-adjusted life years, and net monetary benefit at 12 mo

STATISTICAL METHODS

Sample Size

To achieve 90% power, using simulations based on data from the Oxy-PICU pilot RCT, to detect a clinically meaningful reduction in the mean duration of organ support of 12 hours from 120 to 108 hours and assuming no impact on 7.5% mortality, requires a total sample size of 2,040 patients (allowing for withdrawal/refusal of deferred consent of 10%).

TABLE 3.
Patient Data Collection Schedule

Data	Baseline	At Time of Consent	During Invasive Respiratory Support	End of PICU/ High-Dependency Unit/ Hospital Stay	30 d	90 d	12 mo
Inhospital							
Clinical/baseline data	✓						
Patient/parent details		✓					
Peripheral oxygen saturation, fraction of inspired oxygen, and mean airway pressure[a]	✓		✓				
Organ support[b]			✓	✓	✓		
Discharge data				✓			
Safety monitoring data[c]			✓	✓	✓		
At follow-up							
Survival status				✓	✓	✓	✓
Health-related quality of life (Pediatric Quality of Life Inventory and Child Health Utility-9D)							✓
Health services/resource use					✓		✓

[a]Hourly values for 7 d, then 12 hourly thereafter until the end of invasive mechanical ventilation.

[b]Recorded until patient is discharged home or 30 d after randomization, whichever is sooner. Includes respiratory support, use of vasoactive drugs, extracorporeal membrane oxygenation, blood transfusion, renal support, and sedative drug infusions.

[c]Recorded for all randomized patients from the time of randomization until 30 d after randomization or discharge from PICU, whichever is later.

Internal Pilot

An internal pilot stage will run for the first 6 months of the recruitment period. Data on patients recruited during this period will be analyzed, and the trial will progress from pilot to full trial based on prespecified progression criteria relating to site set up, screening and recruitment, and adherence to the protocol. The final decision on progression from the pilot stage to the full trial will be made by the funder after recommendation, or not, by the Trial Steering Committee (TSC).

Clinical Effectiveness Analysis

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any trial outcomes. Baseline patient characteristics will be compared between the two groups to observe balance and the success of randomization. These comparisons will not be subjected to statistical testing. The primary endpoint will be analyzed using the intention-to-treat (ITT) principle, excluding only those patients where consent to access medical records was withheld or withdrawn before 30-day postrandomization.

The analysis of the primary, composite, outcome will use rank-based methods to test for superiority, with death during the first 30 days following randomization ranked as the worst outcome and surviving patients ranked according to their duration of organ support. The ranked outcomes will be compared between groups using a two-sample rank-sum (Wilcoxon-Mann-Whitney) test with two-sided p value of 0.05. The primary effect estimate will be the probabilistic index (the probability that the intervention is superior to the control for either mortality and/or duration of organ support), which will be presented with a 95% CI. Duration of organ support will be defined as the total number of days on which organ support was given, to day 30, and missing days of support will be handled using multiple imputation. Patients discharged from hospital before 30 days will be assumed to remain alive by 30 days unless otherwise known.

Ordered logistic regression will be used first in a sensitivity analysis to estimate the unadjusted proportional odds ratio and second to estimate the proportional odds after adjusting for the following baseline variables (with missing variables replaced using multiple imputation): age (<12/≥12 mo), primary reason for admission (lower respiratory tract infection vs other), severity of abnormality of gas exchange: Spo_2/fraction of inspired oxygen (Fio_2) ratio less than 221 with positive end-expiratory pressure greater than or equal to 5 versus other, predicted mortality at PICU admission (measured using the Pediatric Index of Mortality 3 score [17]), and site (as a random effect).

Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the following baseline covariates: age (<12/≥12 mo) (18), age-adjusted heart rate, and hemoglobin level at admission.

The interaction effect for continuous covariates (age-adjusted heart rate and hemoglobin at admission) will be illustrated by calculating the adjusted hazard ratio within five categories at quintiles of the continuous variable. The results of subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects (19, 20).

The following secondary sensitivity analyses of the primary endpoint will be performed: 1) excluding patients found to be ineligible following randomization and those where a clinical decision not to follow the trial treatment was recorded immediately postrandomization and 2) with duration of organ support defined as the elapsed number of days from randomization to the last day of organ support to day 30. Unadjusted treatment effects for each of the two components of the composite primary endpoint will be reported, and if the direction of treatment effect differs between components, the partial proportional odds model will be used to estimate adjusted treatment effects.

Secondary analyses of mortality at discharge from critical care and at 30 days will be performed by Fisher exact test. If the number of events allows, logistic regression will be used to compare mortality between groups adjusted for baseline variables.

Duration of survival to 12 months will be plotted as Kaplan-Meier survival curves, comparing unadjusted with the log-rank test and adjusted using Cox regression models. Time to liberation from ventilation will be analyzed by the log-rank test, with patients who die while ventilated treated as censored. Analyses of duration of organ support and PICU and hospital stay will be performed by rank-sum tests, stratified by survival status. Analyses of functional status and HrQoL will be performed by t tests and adjusted linear regression. Baseline factors for inclusion in adjusted analyses will be selected a priori based on an established relationship

with outcome for critically ill children and not because of observed imbalance, significance in univariable analyses, or by a stepwise selection method.

A single interim analysis to compare the primary end point between arms using a two-sided rank-sum test will be undertaken following recruitment and follow-up to 30 days of 50% of patients using a Peto-Haybittle stopping rule ($p < 0.001$) for termination due to either benefit or harm. It will be reviewed by the Data Monitoring and Ethics Committee (DMEC) who will report to the TSC, making recommendations on the continuation, or not, of the trial.

Exposure to the intervention and further treatment patterns by randomized group will be reported using descriptive summary statistics and graphical methods only. The number and percentage of patients with at least one potential protocol deviation (defined as any continuous 3-hr period, where Spo_2 is above or below the target range, and no adjustment has been made to either Fio_2 or mean airway pressure) will be reported and the total number of such deviations.

Integrated Health Economic Evaluation

The cost-effectiveness analysis (CEA) will take a health and personal health service perspective (21). Patient-level resource use data from the PICU stay will be taken from the case report form and linked to routine data from PICANet. PICANet will provide routine data on the level of care for PICU bed-days through collection of the PCCMDS. Information will also be collected on the additional resources (e.g., staff time and medications) required to administer the interventions. Information on subsequent PICU and hospital admissions will be obtained via data linkage with PICANet and Hospital Episode Statistics. Patient-level resource use data will be combined with appropriate unit costs from the NHS payment by results database and Personal Social Services Research Unit to report total costs per patient for up to 12 months since randomization. Use of primary care and community health services will be assessed by questionnaires at 12 months. Data from the PedsQL and CHU-9D questionnaires at 12 months will be combined with survival data to report quality-adjusted life years (QALYs).

The CEA will follow the ITT principle as defined for the clinical effectiveness analysis and report the mean (95% CI) incremental costs, QALYs, and net monetary benefit at 12 months. The CEA will use Bivariate Seemingly Unrelated Regression model to allow for correlation between costs and QALYs. The analysis will adjust for key baseline covariates at both patient and site level using the same adjustments as defined for the clinical effectiveness analysis. The CEA will also perform a cost-consequence analysis and report incremental costs alongside primary outcome at 30 days. Missing data in costs and HRQoL will be handled using multiple imputation methods.

GOVERNANCE AND OVERSIGHT

Research Ethics

Oxy-PICU will be conducted in accordance with the approved trial protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and the Data Protection Act (2018), as well as ICNARC CTU's research policies and procedures.

Confidentiality

Identifiable patient data, including name, contact details, date of birth, and NHS number, will be required by the ICNARC CTU to successfully follow up participants. ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which a participant could be identified. Data will be stored securely and accessed only by trained and authorized staff. ICNARC is registered under the Data Protection Act (registration number: Z6289325), and all ICNARC CTU staff have undergone data protection and ICH GCP training.

Patient and Public Involvement

There was extensive patient and public involvement (PPI) input in the pilot RCT, which informed the procedures for the main trial described here. Additionally, the parent of a child who received respiratory support is among the investigator team and a member of the TMG, and another independent parent representative is a member of the TSC.

Oversight

The TMG is responsible for the management of Oxy-PICU and meets regularly to monitor the conduct and

progress of the trial. It is led by the Chief Investigator and includes the Investigators and the ICNARC CTU trial team. Oxy-PICU is managed by the ICNARC CTU in accordance with the Medical Research Council's Good Research Practice: Principles and Guidelines (22), which is based on the ICH-GCP principles (23) and the U.K. Department of Health's Policy Framework for Health and Social Care Research (24). The on-site monitoring plan will follow a risk-based strategy. A majority independent TSC has been established to monitor trial progress. The committee is comprised of PPI representative, experienced clinicians and researchers, the Chief Investigator, and the Head of Research at ICNARC. An independent DMEC has been established to monitor patient recruitment and retention, adherence, and safety.

ICNARC is the trial sponsor (reference: 17IA05) and holds indemnity and insurance, which will apply for legal liability arising from the design, management, and conduct of the research.

Trial Status

This article presents the protocol (Version 1.3, February 1, 2021) for the Oxy-PICU RCT (25). Due to the COVID-19 pandemic, recruitment (which was due to start February 2020) was postponed, and the trial was paused between March 16, 2020, and July 3, 2020. The first participant was recruited in September 2020. At the time of submission, patient recruitment was ongoing—with recruitment planned to complete in May 2022. Results will be disseminated through publication in peer-reviewed medical journals and at national and international conference.

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Dr. M. J. Peters is Chief Investigator. Ms. Chang and Ms. Orzol are Trial Managers. Ms. Thomas is the Senior Statistician. Ms. Chang, Ms. Thomas, and Dr. M. J. Peters drafted the article. Ms. O'Neill Gutierrez, Dr. Agbeko, Dr. Draper, Dr. Major, Dr. Pappachan, Dr. Ramnarayan, Dr. Ray, Dr. Sadique, Dr. Gould, Dr. Harrison, Dr. Rowan, and Mr. Mouncey are trial coapplicants and members of the Trial Management Group. Mr. S. Peters, Ms. Au, and Dr. Jones supported management of the trial. All authors read and approved the final article.

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Oxy-PICU received Health Research Authority approval (Integrated Research Application System number: 272768) on December 23, 2019, including a favorable ethical opinion from the East of England–Cambridge South Research Ethics Committee (reference number: 19/EE/0362).

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