A Randomised Multiple Centre Trial of Conservative versus Liberal Oxygenation Targets in Critically Ill Children

Please note: This protocol should not be applied to infants and children treated off trial. The trial will be monitored for adverse events and the ICNARC Clinical Trials Unit (CTU) can only ensure that active trial investigators are updated of any amendments to the protocol.

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Chief Investigator
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Sponsor representative
Ms Keji Dalemo

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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For and on behalf of the Trial Sponsor:

Signature: Date:

Name: Keji Dalemo Position: CTU Manager

Chief Investigator:

Signature: Date:

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Abbreviations

AE	adverse event
CRF	case report form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
MRC	Medical Research Council
PaO_2	Arterial partial pressure of oxygen
PICU	paediatric intensive care unit
PIS	Parents/Guardians Information Sheet
REC	Research Ethics Committee
SAE	serious adverse event
SOP	Standard Operating Procedure
SpO_2	Peripherally measured oxygen saturation
TMG	Trial Management Group
TSC	Trial Steering Committee

Summary

Data category	Information
Primary registry and trial identifying number	ISRCTN92103439
Date of registration in primary registry	07/01/2020
Source(s) of monetary or material support	National Institute for Health Research Health Technology Assessment Programme
Primary Sponsor	Intensive Care National Audit & Research Centre
Contact for public queries	Daisy Wiley/Irene Chang Tel: 020 7269 9277 Email: oxypicu@icnarc.org
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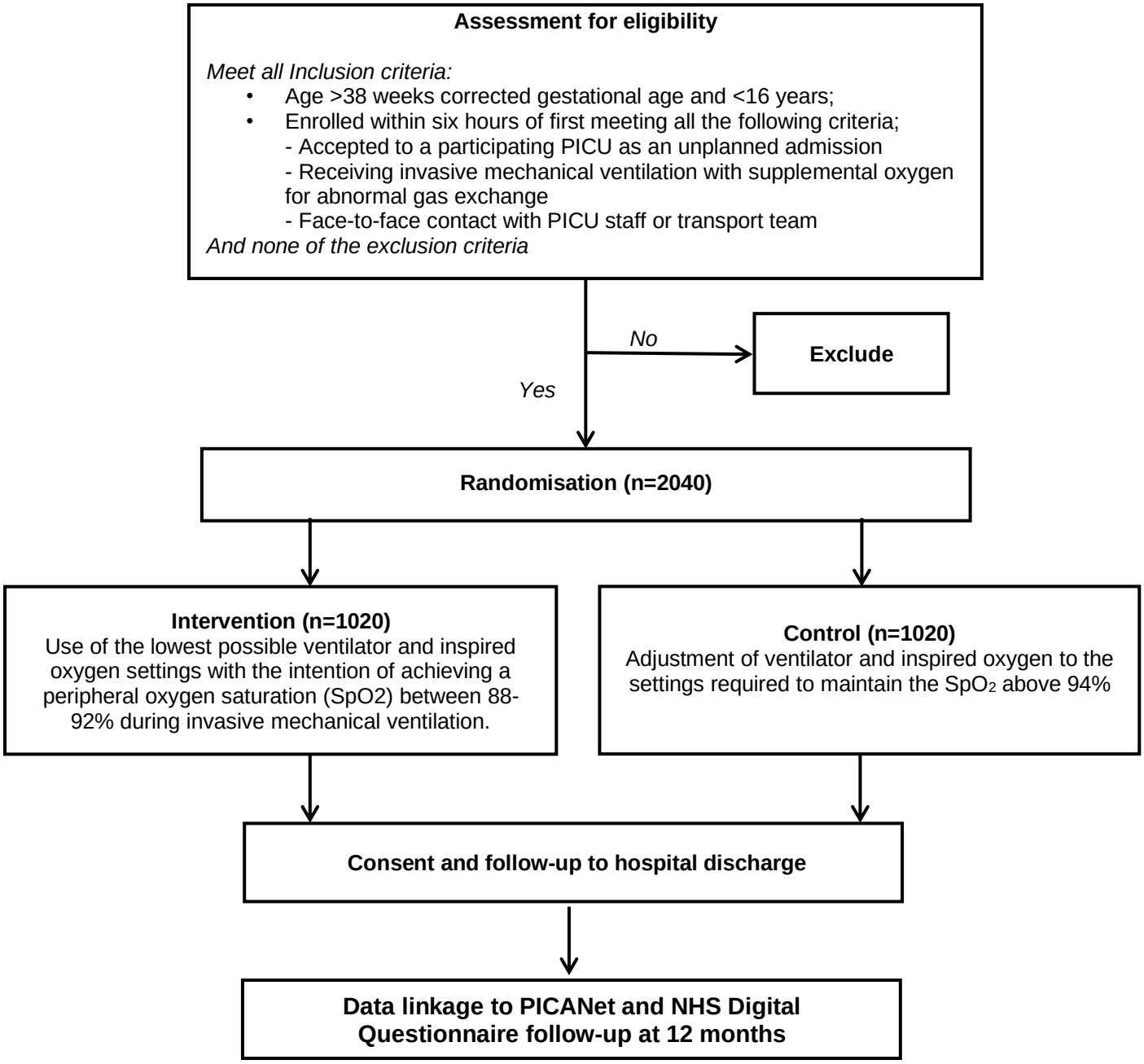
Public title	Oxygen in Paediatric Intensive Care (Oxy-PICU)
Scientific title	Oxy-PICU: A Randomised Multiple Centre Trial of Conservative versus Liberal Oxygenation Targets in Critically Ill Children
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Invasive respiratory support
Intervention(s)	Adjustment of ventilation and inspired oxygen setting to achieve a peripheral oxygen saturation (SpO_2) target of 88-92% during invasive mechanical ventilation
Key inclusion and exclusion criteria	Ages eligible for study: >38 weeks corrected gestational age and <16 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion criteria: 1) Age >38 weeks corrected gestational age and <16 years 2) Enrolled within six hours of first meeting all the following criteria; 3) Accepted to a participating PICU as an unplanned admission 4) Receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange 5) Face-to-face contact with PICU staff or transport team

Data category	Information
	Exclusion criteria: 1) Death perceived as imminent 2) Brain pathology/injury as primary reason for admission 3) Known pulmonary hypertension 4) Known or suspected sickle cell disease 5) Known or suspected uncorrected congenital cardiac disease 6) Receiving long-term invasive mechanical ventilation prior to this admission 7) End-of-life care plan in place with limitation of resuscitation 8) Recruited to Oxy-PICU in previous admission
Study type	Multi-centre, open, parallel group randomised control trial with integrated economic evaluation Interventional Allocation: randomised Blinding: cannot be blinded Phase IV
Date of first enrolment	Anticipated 1 September 2020
Target sample size	2040 infants and children
Primary outcomes	Composite outcome of death and days of organ support at 30-days and incremental costs, quality-adjusted life years and net monetary benefit at 12 months (cost effectiveness)
Key secondary outcomes	1) Mortality at PICU discharge, 30 days, 90 days and 12 months 2) Liberation from ventilation 3) Duration of organ support 4) Functional status at PICU discharge and at 12 months, measured by the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales 5) Length of PICU and hospital stay; 6) HrQoL at 12 months, measured by the child, self-or parent-proxy reported PedsQL-4.0 and the Child Heath Utility 9D (CHU-9D)
Cost effectiveness analysis outcomes	1) Incremental costs at 30 days 2) QALYs and net monetary benefit at 12 months

Figure 1 Trial schema



Contents

1. Background and Rationale

1.1 Background

Around 11,000 of the most seriously ill children are referred to intensive care as an emergency in the UK each year, of whom at least 7,500 receive both invasive mechanical ventilation and supplemental oxygen[1]. The administration of oxygen is a fundamental part of care in paediatric critical illness with supplemental oxygen offered to nearly every acutely unwell child. However, the optimal targets for systemic oxygenation are unknown. Other than in rare cases of congenital heart disease, current practice is to administer supplemental oxygen to achieve arterial oxygen saturations that are at, or above, the normal healthy range.[2] Observational data suggest harm from too generous use of supplemental oxygen in adults[3] and children[4]. However currently, there is no high-quality evidence from randomised controlled trial (RCT) data to support this practice and guide clinicians' use of oxygen. Therefore, there is an urgent need for high quality evidence to inform the choice of oxygen saturation targets in the most seriously unwell children.

1.2 Rationale

Supplemental oxygen therapy is an important target to investigate using as a conservative rather than liberal therapy in critically ill children because:

1) Oxygen is administered to >95% of paediatric intensive care unit (PICU) patients
2) Current practice is to use very high levels of supplementary oxygen to achieve 'normal' or often 'supra-normal' peripheral oxygen saturations (SpO2) of 98-100%.
3) High tissue oxygen being directly harmful in critically ill children is biologically plausible
4) The therapies employed to raise tissue oxygen (mechanical ventilation, transfusion and support for cardiac output) are known to cause harm when used too liberally
5) Currently guidance on oxygen targets is not based on evidence

This uncertainty on targets for supplementary oxygen treatment is relevant to the full age range of children admitted to PICU. Hence our study includes the whole population for whom PICU staff require evidence. The breadth of this range does bring in important developmental and case-mix differences. We are mitigating this by excluding pre-term infants as a physiologically distinct sub-population and plan sub-group analyses of infants compared to older children. One potential confounder is the higher level of foetal haemoglobin (HbF) in young infants which has a different oxygen-haemoglobin dissociation curve and pulse oximetry characteristics. However, in a retrospective sample of over 5000 critically ill children who would be potential candidates for Oxy-PICU recruitment, fewer than 5% of infants >3 months corrected gestational age had HbF at levels likely to have any detectable impact on SpO_2 values. (manuscript in preparation)

1.2.1 Oxygen

Oxygen is a highly reactive element. It is both vital for life and an important potential cause of harm. It has two 'singlet' unpaired electrons in its outer shell which can be either donated to other molecules ('reduction') or can extract electrons to complete the pairs ('oxidation').

The balance between these two processes is known as the 'redox' state of a molecule, cell or tissue.

The redox state determines the structural and functional integrity of many cells as well as individual proteins, lipid and nucleic acids. Alterations in the redox state towards oxidation, referred to as 'oxidative stress', is implicated in many serious chronic diseases including Alzheimer's, motor neurone disease, and atherosclerosis. More recently roles in acute severe illness (sepsis, stroke, myocardial infarction, trauma, acute lung injury) have been described.[5]

Despite this potential for harm, oxygen is essential to life. Oxidation of glucose is the key mechanism for releasing energy from food. This normal '*aerobic'* metabolism describes the conversion of oxygen and glucose to carbon dioxide, water and the high-energy adenosine triphosphate [ATP] molecule). In the absence of sufficient oxygen, a back-up process of '*anaerobic'* metabolism is employed. This is approximately 19-fold less efficient than aerobic metabolism[6]. Signs of tissue anaerobic metabolism are interpreted clinically as 'shock'.

1.2.2 Intensive Care

Ideal intensive care treatment should balance the risks of tissue hypoxia with those of oxidative stress /hyperoxic injury. However, the risk of hypoxia is much more widely appreciated and more easily detected than that of hyperoxia. Indeed, intensive care units have been designed around treatments to prevent, recognise and treat shock by raising tissue oxygen delivery[7]. These include: mechanical ventilation (which can increase oxygen flow into the blood stream); fluid resuscitation and vasoactive drugs use (to raise the cardiac output and blood pressure); and transfusion (to increase oxygen carrying capacity in the blood). Each of these treatments can be lifesaving when the physiology is extremely abnormal.

However clinical trials have shown that each of these treatments (ventilation, transfusion, and possibly fluid resuscitation) are most effective when used more conservatively than standard care. This *'less is more'* concept may be the biggest advance in critical care in the last 25 years and may extend to the routine use of supplemental oxygen.

1.2.3 Evidence from Observational studies

Recent observational studies have shown a 'U-shaped' relationship between arterial oxygenation and case-mix adjusted risk of death[3,8]. We completed a systematic review of the paediatric literature[4] and although the data are scarce, the same pattern of increased risk at both high and low levels of arterial oxygenation has been observed. Our cohort study of 7410 critically ill children demonstrated a 'U-shaped' relationship between arterial oxygen tension at admission and survival[4]. This pattern persisted after adjustment for case-mix (including congenital cyanotic heart disease) and other indicators of physiological severity.

1.2.4 Evidence from Clinical Trials

In April 2018, a systematic review and meta-analysis of 25 randomised controlled trials, including data from 16,037 acutely unwell adults, compared protocols targeting conservative versus liberal concentrations of supplemental oxygen therapy[9]. Its conclusion was that liberal supplemental oxygen therapy was associated with a higher mortality than a more conservative approach (relative risk 1·21, 95% CI 1·03–1·43). The majority of these studies were conducted in acutely ill adults with stroke or ST-elevation myocardial infarction rather than ventilated intensive care patients.

Three trials have reported in critically ill ventilated adult patients. The multi-centre CLOSE pilot study from the ANZICs group compared patients targeted to achieve an SpO_2 of >95% with those targeted to achieve an SpO_2 of 88-92%. In 103 patients, they concluded that a full trial was feasible and that there were no safety concerns[10]. Further, they reported a trend toward reduced mortality with lower SpO_2 targets in the sickest patients: relative risk 0.49 (95%CI, 0.20-1.17; p=0.10). The Oxygen-ICU single centre study of 434 critically ill adults reported a significantly lower ICU mortality with SpO_2 targets of 94-98% when compared to 97-100%: absolute risk reduction 0.086 (95% CI, 0.017-0.150) p=0.01[11]. The Hyper 2S study was stopped for safety reasons with an excess of serious adverse events and a trend towards increased mortality in the hyperoxia group (hazard ratio 1·27, 95% CI 0·94–1·72; p=0·12)[12]. Further trials in adult critical illness are underway around the world.(Table 1)

However, only one group of children has been studied in detail to date: extreme premature infants (<28 weeks gestation, n=4965 across five trials) have been randomised to lower (85%-89%) vs higher (91%-95%) oxygen saturation targets. No net benefit or harm on a combined endpoint of death or major disability was seen at a corrected age of 18 to 24 months. Secondary outcomes of retinopathy of prematurity and necrotising enterocolitis were different but in opposite directions[13]. Risk / benefit profiles from extremely premature infants cannot be extrapolated to older infants or children.

Outside of the intensive care unit Cunningham *et al.*[14] randomised 615 infants and children on paediatric wards with bronchiolitis to SpO_2 targets of >94% or >90%. They showed these targets to be equivalent in terms of safety. However, the lower SpO_2 target was associated with a clinically significant reduction in duration of oxygen therapy: 27.6 (0 to 68.1) hours vs 5.7 (0 to 32.4) hours; hazard ratio 1.37 (1.12 to 1.68), p=0.0021 and time to discharge 50.9 (23.1 to 93.4) vs 40.9 (21.8 to 67.3), p=0.003.

1.3 Pilot and feasibility work

A multicentre pilot RCT was conducted to explore the feasibility of conducting a larger RCT comparing oxygen targets in critically ill children. The results of the pilot work confirmed that it is feasible to conduct a national trial. Design and conduct of the current RCT has been informed by the pilot work.

2. Aims and Objectives

2.1 Aim

The overall aim of Oxy-PICU is to determine if the risks of interventions employed on intensive care to raise peripheral oxygen saturation to >94% exceed their benefits when compared to a peripheral oxygen saturation of 88-92%.

2.2. Objectives

All objectives will evaluate the clinical and cost effectiveness of a conservative peripheral SpO_2 target of 88-92%.

2.2.1 Primary objective

- Composite outcome of mortality and duration of organ support at 30 days (rank-based analysis with death ranked as worse than 30 days of organ support)

2.2.2 Secondary objectives

- Incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 12 months
- Incremental costs at 30 days
- Mortality at PICU discharge, 30 days, 90 days and 12 months
- Time to liberation from ventilation
- Duration of organ support
- Length of PICU and hospital stay
- Functional status at PICU discharge
- Health-related quality of life (HrQoL) at 12 months

3. Trial Design

Oxy-PICU is a pragmatic, open, multiple centre parallel group randomised controlled trial with integrated economic evaluation in infants and children accepted for unplanned admission to a participating PICU.

3.1 Internal pilot

An internal pilot will run from months 7-12 of the grant timeline and use a traffic light system to assess key progression criteria regarding site opening, recruitment and adherence to the study protocol[15]. The internal pilot will follow the same processes as the main trial; participants enrolled in the pilot will be included in the analysis of the main trial.

3.2 Setting

3.2.1 Trial sites

In this protocol, 'site' refers to the 15 NHS paediatric intensive care units (PICU) where the Oxy-PICU Study is conducted. The trial will also work with PIC transport services associated with participating sites.

3.2.1 Site requirements

- Active participation in the Paediatric Intensive Care Audit Network for the UK and Ireland (PICANet) or be able to collect detailed data on patient interventions and outcomes
- Compliance with all responsibilities as stated in the Oxy-PICU Site Agreement;
- Compliance with the study treatments, follow-up schedules and all requirements of the study protocol;
- Compliance with the Research Governance Framework or Policy Framework for Health and Social Care Research and International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP).

3.2.2 Site responsibilities

Sites must:

- Identify a local Principal Investigator (PI);
- Identify an Oxy-PICU Research Nurse responsible for day-to-day local trial coordination;
- Identify a doctor/nurse/allied health professional to act as Oxy-PICU champion in the unit;
- Agree to incorporate Oxy-PICU into routine transport team and PICU activity, particularly highlighting the importance of screening at first contact;
- Agree to adhere to randomisation allocation and to ensure adherence to the protocol; and
- Agree to recruit all eligible patients to Oxy-PICU and to maintain a Screening Log

3.2.3 Site initiation and activation

The following documentation must be in place prior to a site being activated for recruitment:

- A completed site initiation visit with adequate attendance to ensure knowledge of Oxy-PICU can be disseminated throughout the unit
- All relevant institutional approvals (e.g. confirmation of capacity and capability);
- A fully signed Oxy-PICU Site Agreement; and
- An up-to-date Delegation Log.

Once the ICNARC CTU have confirmed that all documentation is in place, a site activation e-mail will be issued to the site PI, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- Adherence to the most recent approved version of the protocol;
- All relevant site staff are trained in the protocol requirements and, where necessary, meet Good Clinical Practice requirements;

- Appropriate recruitment and care for patients in the study;
- Timely data entry and validation; and
- Prompt notification of all Adverse Events (as specified in Section 5).

All local staff involved in the conduct of the study must be authorised on the Oxy-PICU Delegation Log once trained to carry out their assigned roles. This Log should be held at site and copied to the ICNARC CTU when any changes are made.

Per the MHRA/HRA *Joint Statement on the Application of Good Clinical Practice to Training for Researchers*, members of the study team involved in screening, randomisation and wider study activities (such as providing the intervention) should be provided with study-specific training to carry other these tasks. They do not require specific GCP training.

3.2 Population

The target population is infants and children requiring mechanical ventilation with supplemental oxygen for abnormal gas exchange.

3.2.1 Inclusion

- Less than 16 years and more than 38 weeks corrected gestational age
- Enrolled within six hours of first meeting all the following criteria;
    - Accepted to a participating PICU as an unplanned admission
    - Receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange
    - Face-to-face contact with PICU staff or transport team

3.2.2 Exclusion

- Not expected to survive to ICU admission
- Brain pathology/injury as primary reason for admission (e.g. traumatic brain injury, post-cardiac arrest, stroke, convulsive status epilepticus without aspiration)
- 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 invasive mechanical ventilation prior to this admission
- Recruited to Oxy-PICU in a previous admission

3.2.3 Co-enrolment

The SMG will consider co-enrolment of Oxy-PICU participants onto other interventional studies where the management does not conflict with the Oxy-PICU objectives on a case-by-case basis. Participants will be permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies). Details of any co-enrolment will be documented on the Oxy-PICU enrolment log.

3.2.4 Screening

Potentially eligible infants and children admitted/accepted for admission to the participating unit will be screened against the inclusion/exclusion criteria by the local clinical or transport team. Patients who are eligible but not randomised, or who fulfil all the inclusion criteria but meet one or more of the exclusion criteria, will be recorded in the Oxy-PICU Screening Log.

3.3. Recruitment and Consent

3.3.1 Pre-recruitment care

Prior to recruitment, all care will be determined by the clinical team primarily responsible for the child's treatment and care.

3.3.2 Randomisation

Randomisation must occur as soon as eligibility has been confirmed with the aim of commencing treatment as soon as possible within the first six hours of the infant or child being in face-to-face contact with the Paediatric Intensive Care or Transport Staff. Patients will be randomised on a 1:1 basis to either the liberal (>94%) or conservative (88-92%) SpO_2 target using a central telephone/web-based randomisation service. The service will be available 24 hours a day, seven days a week.

The randomisation sequence will be a computer-generated dynamic procedure (minimisation) with a random component. Minimisation will be performed on: age (<12 months / ≥12 months); site; primary reason for admission (lower respiratory tract infection vs. Other); and severity of abnormality of gas exchange: SF ratio <221 with PEEP ≥5 vs. Other. Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability.

The staff member who randomised the patient is responsible for informing the clinical team responsible for the patients care of the randomisation. Site teams are responsible for establishing robust procedures to ensure this information is not missed (e.g. at handover from transport team to unit staff). The local site research team will be notified of the enrolment by email. Following randomisation, each participant will be assigned a unique Oxy-PICU trial number and CRF to be completed by the local site research team.

During the recruitment period, a member of the Oxy-PICU study team will be available to address emergency recruitment and randomisation issues on 020 7269 9295.

3.3.3 Consent procedures

Children who are eligible for Oxy-PICU will often become so during a period of life-threatening illness. This is a profoundly stressful situation for parents/guardians during which time there are ethical concerns both about the burden placed of trying to understand the trial and their ability to provide informed consent during a time of great distress. Furthermore, any delay in commencing treatment would be detrimental to the child's care.

Oxy-PICU will use a deferred consent model ('research without prior consent'). Once a patient is identified as being eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment will be commenced as soon as possible.

This model, developed in line with CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance[16-17], is acceptable to parents/guardians as well as to clinicians[17-21]. Our approach is also informed by experience and feedback from the Oxy-PICU pilot study. As part of the pilot RCT, we asked parents of children who were randomised to the study for their feedback. This included feedback on: the timing and content of the approach; the use of 'research without prior consent'; the Parent Information Sheet; the format of discussions; and decision making. Findings from this survey have been incorporated into our consent procedures and will be used for training at sites.

3.3.3.1 Consent prior to hospital discharge

Once notified of the randomisation of a patient to the study, a delegated member of the site research team will approach the parents/legal guardian to discuss the study as soon as practical and appropriate. This will usually be within 24-48 hours of randomisation. If the patient has died or been discharged prior to their parents/legal representatives being approached, then the parents/legal guardians will be approached at a later point (see *Death prior to consent being sought* and *Discharge prior to consent being sought*).

Before approaching the parent/legal guardian, the research team member will discuss with the clinical staff that the patient is stable and that the timing is appropriate. If the patient's condition has not stabilised or the clinical team feel it is not an appropriate time, additional time should be allowed before approaching the parent/legal representative. These discussions should be recorded in the patients' clinical notes.

Once approached, a Participant Information Sheet (PIS) for parents/legal guardians will be provided. The PIS will identify the title of the study and the Chief Investigator (CI), and include information about: the purpose of the study; the implications of participating or not; participant confidentiality; use of personal data; data security; and the future availability of the results of the study.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection. Parents/legal guardians will be allowed time to read the PIS and have an opportunity to ask any questions they may have about their child's participation in Oxy-PICU.

After the person seeking consent has checked that the PIS and Consent Form are understood, they will invite the parent/legal guardian to sign the Consent Form and will then add their own name and countersign. A copy will be given to the parent/legal guardian, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to age and the severity of illness and its impact on mental state of the target population, it will not be possible to involve study participants in the consenting process. Instead, assent will be obtained prior to hospital discharge if their condition allows. Study participants will then be provided with an age appropriate PIS and asked to sign an Assent Form, if appropriate. Parents/legal representatives will be involved in this discussion. If the participant is likely to regain capacity following hospital discharge, then an age appropriate PIS will be provided to parents/legal representatives to discuss with the participant following recovery.

3.3.3.2 Discharge prior to consent being sought

In the unlikely situation where a participant is discharged from hospital before consent has been sought or confirmed, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal guardians within five working days of hospital discharge to inform them of the participant's involvement in the study and provide details of the study. Following on from the call, as well as if there is no response to the call, the parents/legal guardians will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the PIS and Consent Form by post. Where possible, the clinical team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the information sheet for detailed information on the study and provide telephone contact details if parents/legal representatives wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the PIS and Consent Form will be sent. This second letter will provide the same information as the first letter but will confirm that if no Consent Form is received within four weeks of the second letter being sent, then the participant's data will be included in the study unless the family notify the site research team otherwise. In this event, the site research team should document the non-response on a File Note in the Investigator Site File.

If the participant is transferred to another hospital participating in Oxy-PICU before the consent procedures are complete, then the originating research team will hand-over to the receiving hospital.

3.3.3.3 Death prior to consent being sought

In the rare situation where a participant dies before consent has been sought, a site research team member will obtain information from colleagues and bereavement counsellors to establish the most appropriate research team member to notify the parents/legal guardians of the involvement in the research study. Deferred consent can be sought from parents/legal guardians following the death of their child and prior to their departure from the hospital; however, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Participant Information Sheet for bereaved parents/legal guardians (B-PIS) and Consent Form would be used.

If deferred consent is not sought prior to the parents'/legal guardian's departure from the hospital, then they will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the B-PIS and Consent Form (version for bereaved parents/legal representatives) by four weeks after randomisation. Where possible, the clinical team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the B-PIS for detailed information on the study and provide telephone contact details if parents/legal guardian wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the B-PIS and Consent Form (version for bereaved parents/legal representatives) will be sent to the family. This second letter will provide the same information as the first letter but this letter will also confirm that if no Consent Form is received within four weeks of receipt of the letter, then the participant's data will be included in the study unless the family notify the site research team otherwise.

3.3.3.4 Non-consent/Withdrawal

In consenting to the study, parents/legal representatives are consenting to the data already collected (on the study treatment and assessments) to be used and to follow-up. However, parents/legal representatives can refuse to give consent (non-consent) or withdraw from Oxy-PICU at any time during the study. If a parent/legal representative explicitly states that they no longer wish for their child to take part or to contribute further data to the study, their decision must be respected. The date of withdrawal of consent and any reason, if provided, should be recorded onto the secure data entry system. A File Note documenting the withdrawal should be created and filed in the Investigator Site File.. Withdrawal of a child from the study should be recorded in their medical notes and no further data collected. All data collected up to the point of withdrawal will be retained and included in the study analysis.

In order to monitor non-consent, a minimal dataset will be collected for each parent/legal representative approached but not consented: a) Study site; b) Date/time randomised; c) Randomised intervention (including whether started on assigned treatment or not); d) Reason not consented (if parents/legal representatives are willing to provide reason for non-consent).

3.4 Outcome Measures

3.4.1 Internal pilot

We will use a traffic light system to assess progression from pilot stage to the full trial as below:

	Green	Amber	Red
Number of sites open to recruitment	≥10	6-9	<6
Recruitment rate (per site per month)	≥4.5 (≥75% of anticipated)	3-4.5 (40-75% of anticipated)	<3 (<40% of anticipated)

Separation in mean measurements between groups	SpO_2: ≥3% OR FiO_2 concentration: ≥0.1	SpO_2: 1.5-3% OR FiO_2 concentration: 0.05 – 0.09	SpO_2: <1.5% OR FiO_2 concentration: <0.05
Treatment adherence – carried out per protocol	≥75% cases	50-75% cases	<50% cases

3.4.2 Main trial

Primary outcome
Composite outcome of death and days of organ support at 30 days (clinical effectiveness) and incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 12 months (cost effectiveness).

Secondary outcomes
- Incremental costs at 30 days
- Mortality at PICU discharge, 30 days, 90 days and 12 months
- Time to liberation from ventilation
- Duration of organ support
- Length of PICU and hospital stay
- Functional status at PICU discharge
- Health-related quality of life (HrQoL) at 12 months

3.5 Trial treatment

Intervention
Adjustment of ventilator and inspired oxygen to the lowest settings/concentrations with the intention of achieving a peripheral oxygen saturation (SpO_2) between 88-92% where possible during invasive mechanical ventilation.

Comparator
Adjustment of ventilator and inspired oxygen to the settings required to maintain the SpO_2 above 94%.

End of treatment
For both groups, trial treatment will continue until mechanical ventilator support with supplemental oxygen has been discontinued during the PICU admission. The trial treatment will apply at any point the patient requires mechanical ventilation during their PICU admission (for example, the patient will return to their assigned treatment group in the case of failed extubation). The decision to discontinue mechanical ventilation with supplemental oxygen is at the discretion of the clinical team.

As a pragmatic study, the choice of settings to achieve the SpO_2 target and all other care is at the discretion of the clinical team.

Co-interventions
All other care (including antimicrobial therapy, fluid therapy, analgesia and sedative agents, bronchodilator therapy) will be determined by the clinical team primarily responsible for the participant's care.

3.6 Questionnaire follow-up

Each participant will be followed up with a questionnaire at 12 months post-randomisation to assess HrQoL. Prior to the sending of a questionnaire, survival status will be ascertained either through review of medical records by local research teams and/or via data-linkage with nationally held records (decedents will be logged in the trial records and the follow-up process ended).

At the 12-month time point, parents/legal guardians of recruited patients will be emailed or posted (as per their preference indicated at the time of consent) a questionnaire by the ICNARC CTU containing the PEDS-QL and CHU-9D). The questionnaires are designed to take no longer than 15 minutes to complete. If a parent requests a questionnaire to be sent via post, then a pen and self-addressed stamped envelope will be provided for ease of return.

If there is no response within three weeks, parents/legal guardians will be telephoned and asked to confirm whether they have received the questionnaire. If needed, they will be offered the option of either being sent another copy of the questionnaire (via email or post), or to complete the questionnaire over the telephone with a trained member of the Oxy-PICU trial team.

If a patient is an in-patient at a participating site at the follow-up time-point, the site research team will be asked to approach the parent/legal guardian and, if willing, conduct the questionnaire with the parents/legal guardians in hospital.

3.7 Safety Monitoring and Reporting

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

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

3.7.1 Adverse Event

An Adverse Event (AE) is defined as: any untoward medical occurrence or effect in a patient participating in a study.

3.7.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an Adverse Event that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;

- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect.

"Life-threatening", in the definition of a Serious Adverse Event, refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

"Hospitalisation" refers to inpatient admission, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

3.7.3 Unexpected and Related Serious Adverse Event

A suspected Adverse Event related (possibly, probably or definitely) to the trial treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

3.7.4 Assessment

The PI, or other medically qualified investigator as listed on the Delegation Log, should assess severity, relatedness, and expectedness, categorised as follows:

3.7.4.1 Severity

- **None**: indicates no event or complication.

- **Mild**: complication results in only temporary harm and does not require clinical treatment.

- **Moderate**: complication requires clinical treatment but does not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitation to the participant.

- **Severe**: complication requires clinical treatment and results in significant prolongation of hospital stay, permanent functional limitation.

- **Life-threatening**: complication that may lead to death or where the participant died as a direct result of the complication/adverse event.

3.7.4.2 Relatedness

- **None**: there is no evidence of any relationship to the study treatment.

- **Unlikely**: There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the participant's clinical condition, other concomitant medications).

- **Possibly**: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).

- **Probably**: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

3.7.4.3 Expectedness

- **Expected**: the event is listed as an expected AE in Appendix 2.

- **Unexpected**: the event is not listed as an expected AE in Appendix 2.

3.7.5 Recording and Reporting procedures

Occurrences of the specified, expected adverse events will be recorded for all randomised patients from the time of randomisation until 30 days after randomisation or discharge from PICU, whichever is later.

Considering that all children eligible for Oxy-PICU are critically ill and, due to the complexity of their condition, are at an increased risk of experiencing AEs – occurrences of non-specified, unexpected adverse events will only be reported if they are considered to be related to the study treatment (possibly, probably or definitely).

The following events will not be reported as AEs or SAEs as they are collected as study outcomes:

- Organ support
- Death (death itself should not be reported as an SAE, but the suspected cause of death should be assessed for severity, relatedness and expectedness).

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported to ICNARC CTU using the Oxy-PICU SAE Reporting Form within 24 hours of the site research team becoming aware of the event. Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available.

SAEs must be recorded in the patients' medical notes, on the Oxy-PICU CRF, and reported to the ICNARC CTU using the Oxy-PICU SAE Reporting Form, by email to oxypicu@icnarc.org or

by uploading the form into the secure web-based data entry system, within 24 hours of observing or learning of the SAE(s). The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1.

On receipt of an SAE report, a member of the ICNARC CTU will first evaluate the report for completeness and internal consistency. Then, a clinical member of the Oxy-PICU Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated by either the Chief Investigator or a clinical member of the Oxy-PICU TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Data Monitoring and Ethics Committee (DMEC) on a basis deemed appropriate by the DMEC.

3.7.6 Notifying the Research Ethics Committee

Adverse Events that do not require expedited reporting to the REC will be reported annually to the REC. This will commence annually from the date of REC favourable ethical opinion for the trial.

3.8 Data collection

To maximise the efficiency of the design, data collection for Oxy-PICU will be nested within the routine data collection for the PICANet audit. Data from PICANet used in the trial analysis will include:

- baseline demographics and risk factors, including the Paediatric Index of Mortality score;
- secondary outcomes of PICU mortality, duration of PICU and acute hospital stay; and
- critical care daily interventions (and associated costs), based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.

All patients recruited to the trial will be informed regarding data linkage with other routine data sources. Data obtained from routine data sources will include:

- date of death for deaths occurring after discharge from acute hospital, by data linkage with death registrations (NHS Digital); and
- hospital costs for subsequent hospitalisations, by data linkage with Hospital Episode Statistics (NHS Digital).

Additional data items collected specifically for the trial will be limited to the minimum required to deliver the trial objectives. These will include:

- name, address and telephone number for questionnaire follow-up;
- data items to confirm eligibility;
- data to monitor adherence with the treatment protocol, including SpO_2 and FiO_2

- time to extubation; and
- adverse event reporting.

Data will be recorded in trial case report forms at participating sites and will be entered at site onto an electronic case report form (secure data entry system setup at ICNARC CTU), where they will undergo checks for accuracy, completeness, and consistency.

3.9 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper CRFs will be available to participating sites. The site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PI to qualified members of the research team, on the understanding that the site PI retains responsibility for the data collection oversight.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy, and consistency of data. Queries on incomplete, inaccurate, or inconsistent data will be sent to the local research team at participating sites for resolution. The local PI will be responsible for ensuring all queries are addressed and for overall quality of their site data.

Security of the electronic data entry system is maintained through usernames and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018.

3.10 Monitoring and Auditing

3.10.1 Central monitoring

The trial team members at ICNARC CTU will have regular communications with sites via email, telephone, teleconferences, and newsletters. Adherence to the protocol will be paramount in the central monitoring plan, including review of consent forms, eligibility data and adherence to the trial arm target.

3.10.2 Site monitoring

The on-site monitoring plan will be developed following a risk-based strategy. Selected sites will be visited at an early stage. The timing and frequency of visits to sites will be based on a risk assessment, including an assessment of the sites and local research team (e.g. experience of multicentre research, involvement in RCTs etc.). It is anticipated that 25% of sites will be visited at least once during the recruitment period to monitor and discuss adherence to the trial protocol and standard operating procedures. Directly following all site visits, the site PI will be verbally advised of the core monitoring findings and this will be followed with a written a report to the site summarising the visit, documents reviewed and any findings. Information learnt at site visits will be used to refine standard operating procedures, as required, ensuring clarity and consistency across sites.

3.11 Statistical Analysis

3.11.1 Sample size

The primary outcome will be analysed using rank-based methods, with death at 30 days ranked as the worst outcome. 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 2040 patients (allowing for withdrawal/refusal of deferred consent of 10%) A single interim analysis will be undertaken.

3.11.2 Internal pilot

Data will be analysed at the end of the internal pilot trial stage (months 7-12 of the grant timeline) on patients recruited during the first six months of the trial. The analysis will take place in month 14 of the grant to allow data to be collected and entered to assess all progression criteria. The objectives of the feasibility analysis will be to assess whether there has been successful site set-up, screening and recruitment, and adherence to the protocol. The RCTs will progress from the pilot stage to full trial based on the progression criteria (see section 2.4.1). Where any of the progression criteria are given an 'Amber light', a management plan will be put in place by the TMG and discussed with the Trial Steering Committee (TSC). The final decision on progression from the pilot stage to the full trial will be made by the NIHR HTA programme after recommendation, or not, by the TSC.

3.11.3 Clinical effectiveness analysis

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. All analyses will follow the intention to treat principle. Baseline patient characteristics will be compared between the two groups to observe balance and the success of randomisation. These comparisons will not be subjected to statistical testing. The delivery of the intervention will be described in detail.

The analysis of the primary, composite, outcome will use rank-based methods, with death during the first 30 days following randomisation 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. 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% confidence interval.

Secondary analyses of mortality will be performed by Fisher's exact test and adjusted logistic regression. Duration of survival to 12 months will be plotted as Kaplan-Meier survival curves, compared unadjusted with the log rank test and adjusted using Cox regression models. Time to liberation from ventilation will be analysed 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 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.

3.11.4 Integrated health economic evaluation

The cost effectiveness analysis (CEA) will take a health and personal health services perspective. 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, medications etc.) required to administer the interventions. Information on subsequent PICU and hospital admissions will be obtained via data linkage with PICANet and Hospital Episode Statistics. This has been highly efficient in our recent FiSh (HTA Project: 13/04/105) and FEVER (HTA Project: 15/44/01) trials. 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 randomisation. Use of primary care and community health services will be assessed by questionnaires at 12 months. Data from the PedsQL and Child Heath Utility 9D (CHU-9D) questionnaires at 12 months will be combined with survival data to report QALYs.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 12 months. The CEA will use multilevel linear regression models that allow for clustering of patients at site. The analysis will adjust for key baseline covariates at both patient and site level.

The CEA will also perform a cost-consequence analysis and report incremental costs alongside primary outcome at 30 days. ICNARC and the London School of Hygiene and Tropical Medicine have combined on a number of economic evaluations maximising the use of routine data alongside questionnaire data for NIHR-funded critical care trials (e.g. ProMISe HTA Project: 07/37/47; and CALORIES, HTA Project: 07/53/03).

3.11.5 Study Within A Trial

We recently completed the NIHR funded FEVER Feasibility Study (HTA Project: 15/44/01). Results from the mixed-methods integrated perspective part of this study (which sought site staff views on the study procedures) revealed that site staff who received study training from the Chief Investigator (CI) felt more prepared for recruitment and consent procedures, and had greater ‘buy-in’ to both the trial protocol and intervention, which ultimately may have impacted on adherence to the study protocol and procedures. Consequently, reviewers identified the need to explore good practice education and training modules to promote engagement with research and protocol adherence as a future research

recommendation in-line with the findings of this project. Within Oxy-PICU, we propose to conduct a Study Within a Trial (SWAT) evaluating the impact of an additional onlineeducation and training package on protocol adherence, staff engagement, and staff confidence in recruitment and consent procedures. We will randomise sites at a cluster level (1:1) to intervention (site initiation training plus education and training package) or control (site initiation training and materials alone). Intervention sites will receive an enhanced training and education package in addition to a site initiation visit conducted by the CI while control sites will receive a site initiation visit alone.

4. Ethics, approvals and dissemination

4.1 Research ethics

Oxy-PICU will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the UK Data Protection Act 2018 as well as the ICNARC CTU research policies and procedures.

4.1.1 Trial registration

The trial has been registered with ISCRCTN - ISRCTN92103439

4.1.2 Central NHS ethical compliance

The trial has received favourable ethical opinion from the East of England – Cambridge South Research Ethics Committee (ref: 19/EE/0362) and approval from the Health Research Authority (IRAS: 272768)

4.1.3 Local ethical compliance

It is the responsibility of the site PI to obtain the necessary local approvals for Oxy-PICU, including formal confirmation of capacity and capability. Evidence of confirmation of capacity and capability at each participating site must be provided prior to site activation.

4.2 Protocol amendments

The study will be conducted in accordance with the current approved version of the Protocol. Any proposed amendments to the research will be considered by the Sponsor in the first instance and then categorised as either substantial or minor and the research protocol modified accordingly. Agreed amendments will be submitted to NHS ethics and/or HRA dependent on the categorisation and, following approval, the amendment will be implemented in accordance with HRA guidance.

4.3 Confidentiality

Identifiable patient data, including name, contact details, date of birth and NHS number, will be required by 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 participant could be identified. Data will be stored securely.

All data will be securely stored in a locked cabinet or in an encrypted electronic file. ICNARC is registered under the Act (Reg: Z6289325) and will preserve the confidentiality of participants taking part in the study.

4.4 Declaration of interests

The Oxy-PICU investigators report no conflicts of interest.

4.5 Dissemination

The results of Oxy-PICU will be disseminated actively and extensively. The research team has strong links with the paediatric critical care community via the Paediatric Intensive Care Society (PICS), PICS Study Group (PICS-SG), and the NIHR CRN: Children Clinical Studies Group (CSG) in Anaesthesia, Intensive Care and Cardiology, and similarly with the nursing community through the British Association of Critical Care Nurses (BACCN), the Royal College of Nursing Critical Care and In-flight Nursing Forum (RCN CCINF) and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). We also have links with the Healthcare Quality Improvement Partnership national audit programme through the Paediatric Intensive Care Audit Network (PICANet).

Social media will be used to actively publicise progress with the research and disseminate our findings. The findings from our work will be presented at national and international conferences. A Study Report to the NIHR HTA Programme will present a detailed description of the project and the results along with recommendations for future policy, practice and research.

The study findings will also be published in high-impact, open-access, peer reviewed scientific journals and relevant professional journals. The results of the study will be disseminated to patients and their families, facilitated by the co-applicants, members of the research team who have links with PICS and the NIHR CSG, and via Family Groups we have liaised with already.

4.5.1 Data Sharing

We will make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. Once the data from the study are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.

5. Trial Closure

5.1 End of trial

The end of trial will be defined as when the last participant has completed follow-up (last participant, last follow-up). At this point, the ICNARC CTU will submit the ‘Declaration of end of trial’ to the REC.

5.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will archive securely all centrally held trial-related documents for a minimum of 15 years in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The Site PI will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of 15 years after the end of the trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and to show whether the unit complied with the principles of ICH GCP and other applicable regulatory requirements.

Guidance on archiving will be provided in the trial-specific SOP. All archived documents, centrally and locally, should be available for inspection by appropriate authorities upon request.

5.3 Early discontinuation of the trial

The trial may be stopped early upon recommendation of the TSC, in which case the ICNARC CTU will inform all relevant staff working on Oxy-PICU and advise on the actions to be taken as regards the treatment of participants. All randomised participants will continue to be followed up as per the Oxy-PICU Protocol.

6. Trial management and committees

6.1 Good research practice

Oxy-PICU will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice: Principles and Guidelines[22] based on the principles of the International Conference on Harmonisation guidelines on Good Clinical Practice[23]. The ICNARC CTU has developed its own policies and procedures, based on these guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

6.2 Trial Management Group

The TMG will comprise the Oxy-PICU investigators, led by the Chief Investigator. The day-to-day trial team will comprise the Chief Investigator, CTU co-investigators and the Trial Manager, Trial Statisticians, Research Assistant and Data Manager.

The TMG will meet regularly to discuss management and progress of the trial and findings from other related research.

6.3 Trial Steering Committee

The TSC will be established in accordance with the NIHR HTA guidelines. The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure the trial is conducted in accordance with the rigorous standards set out in the UK Framework for Health and Social Care research and the Guidelines for Good Clinical Practice. The TSC will

be comprised of a majority of independent members, chaired by Professor Robert Tasker, and will include a Patient and Public Involvement representative.

6.4 Data Monitoring and Ethics Committee

The DMEC will operate under the DAMOCLES Charter, and will report to the TSC, making recommendations on the continuation, or not, of the trial. Safety will be monitored by the DMEC through mandatory reporting of SAEs throughout the trial period.

6.5 Role of the ICNARC Clinical Trials Unit

The ICNARC CTU will be responsible for the day-to-day management of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are reported, as appropriate, to the REC.

7. Sponsorship and Funding

7.1 Sponsorship and indemnity

ICNARC is the sponsor for Oxy-PICU. ICNARC holds Professional Indemnity insurance (Policy number: A05305/0816) and Excess Professional Indemnity insurance (Policy number: Epic 50548A / ExLayer1 / 10691144). These indemnities meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.

7.2 Funding

Oxy-PICU is funded by National Institute of Health Research Health Technology Assessment NIHR127547

A written agreement with the site PI and/or the PI's institution and the Intensive Care Audit and Research Centre (ICNARC) will outline the funding arrangements to sites. The TSC will meet and review the financial aspects of the trial at least annually and report to the Sponsor.

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Appendix 1 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA04	1.2	07 Aug 2020	Sam Peters	Changing order of inclusion criteria for further clarification
NSA09	1.3	01 Feb 2021	Irene Chang	Clarification of adverse event reporting period and procedure for recording withdrawals; correcting typos and reference to follow-up questionnaire; removing references to incorrect documents

Appendix 2: Expected adverse events

New onset of severe lactic acidosis (>5mmol/L) without otherwise known cause

New onset of cardiac ischaemia without otherwise known cause

New onset of acute kidney injury without otherwise known cause

New onset of seizures without otherwise known cause

[This list is not exhaustive. If an adverse event, as defined in section 3.7.3, occurs this should be recorded and reported as described in section 3.7]