Great Ormond Street Hospital for Children NHS Foundation Trust

icnarc intensive care national audit & research centre

Oxy-PICU

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

Research Ethics Committee reference:	16/SC/0617
Trial Sponsor:	Great Ormond Street Hospital for Children NHS Foundation Trust
Sponsor reference:	15IA35
ClinicalTrials.gov reference:	NCT03040570
Trial Funder:	Great Ormond Street Hospital Children's Charity, Registered Charity No. 235825
IRAS number:	212228
Protocol version:	1.1
Protocol version date:	1 December 2016

Chief Investigator:
Prof Mark Peters
Professor of Paediatric Intensive Care
and Hon Consultant Intensivist
The UCL Great Ormond Street Institute of Child Health

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.

Trial Sponsor

Sponsor representative: Emma Pendleton
Deputy Director of Research & Innovation
Joint Research and Development Office
Division of Research and Innovation
Great Ormond Street Hospital for Children
NHS Foundation Trust &
The UCL Great Ormond Street Institute of Child Health
2nd Floor, 30 Guilford Street
London WC1N 1EH
Email: research.governance@gosh.nhs.uk

Trial Management

Chief Investigator: Prof Mark Peters
Professor of Paediatric Intensive Care and Hon Consultant Intensivist
Respiratory, Critical Care and Anaesthesia Unit
The UCL Great Ormond Street Institute of Child Health
30 Guilford Street
London WC1N 1EH
Secretary: 020 7829 7950
Mobile: 07968 188226
Email: mark.peters@ucl.ac.uk

Clinical Trials Unit: Daisy Wiley
Trial Coordinator
Clinical Trials Unit
Intensive Care National Audit & Research Centre
Napier House
24 High Holborn
London WC1V 6AZ
Telephone: 020 7269 9277
Fax: 020 7831 6879
Email: oxypicu@icnarc.org

Study investigators

Name	Department	Organisation
Professor Mark Peters	Paediatric Intensive Care Unit	University College London Great Ormond Street Institute of Child Health
Dr Padmanabhan Ramnarayan	Children's Acute Transport Service	Great Ormond Street Hospital for Children NHS Foundation Trust
Professor Mike Grocott	Clinical and Experimental Sciences, Faculty of Medicine	University of Southampton
Dr David Harrison	Clinical Trials Unit	Intensive Care National Audit & Research Centre
Professor Kathy Rowan	Clinical Trials Unit	Intensive Care National Audit & Research Centre
Paul Mouncey	Clinical Trials Unit	Intensive Care National Audit & Research Centre
Dr Simon Eaton	Developmental Biology and Cancer	University College London Great Ormond Street Institute of Child Health
Dr David Inwald	Paediatric Intensive Care Unit	St Mary's Hospital Paddington
Dr Jon Pappachan	Paediatric Intensive Care Unit	Southampton General Hospital
Dr Sainath Raman	Paediatric Intensive Care Unit	Great Ormond Street Hospital for Children NHS Foundation Trust
Nadav and Sharon Heinoch	Parents of patient recently admitted to Paediatric Intensive Care Unit	Patient, Carer and Public Involvement and Engagement

Contents: **Page No**

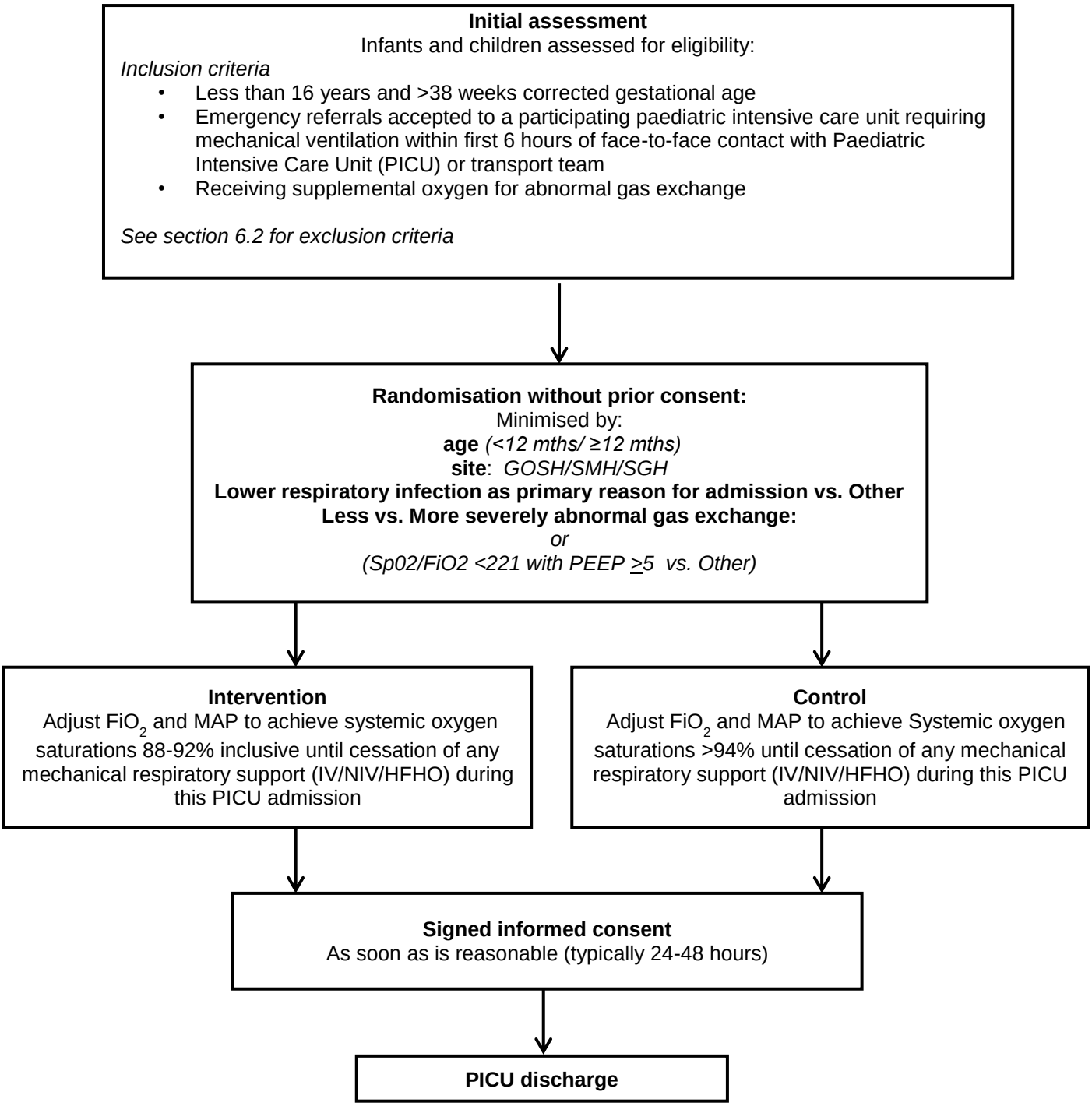
Abbreviations

AE	adverse event
ARDS	acute respiratory distress syndrome
CPAP	continuous positive airways pressure
CRF	case report form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
FiO_2	fraction of inspired oxygen
GOSH	Great Ormond Street Hospital for Children
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
P/F ration	ratio of PaO2 to fraction of inspired oxygen
PICU	paediatric intensive care unit
PIM2	Paediatric Index of Mortality version 2
PIS	Parents/Guardians Information Sheet
REC	Research Ethics Committee
SAE	serious adverse event
$ScvO_2$	central venous oxygen saturation
SOP	Standard Operating Procedure
SaO_2	Arterial oxygen saturation
SpO_2	Peripherally measured oxygen saturation
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London

1.0 Protocol Summary

Title:	A Randomised Pilot Multiple Centre Trial of Conservative versus Liberal Oxygenation Targets in Critically Ill Children
Short Title/acronym:	Oxy-PICU
Research Ethics Committee number:	16/SC/0617
Sponsor name & reference:	Great Ormond Street Hospital for Children NHS Foundation Trust, 15IA35
Funder name & reference:	Great Ormond Street Hospital for Children's Charity, Registered Charity No. 235825
Clinicaltrials.gov reference:	NCT03040570
Design:	Pragmatic, open, randomised controlled pilot trial
Overall aim:	a) To determine the feasibility of a large scale randomised controlled trial comparing a conservative oxygen saturation target (88-92%) with a more liberal target (>94%) b) To determine the safety of a conservative oxygen saturation target (88-92%) with a more liberal target (>94%)
Primary outcome:	The number of eligible patients recruited to the study
Secondary outcome:	a) the feasibility of the proposed model of randomisation without prior parental consent b) whether it is feasible to randomise at least 50% of eligible patients to the study c) the distribution of time to randomization d) the proportion of systemic oxygen saturations within the target range in each group e) staff adherence to protocols f) the proportion of patients in each arm requiring other treatments influencing tissue oxygen delivery (blood transfusion, inotropic support) g) the distribution of potential primary endpoints for a definitive study including: length of ventilation, length of PICU stay, PICU mortality, hospital mortality, duration of individual organ support.
Target accrual:	120 infants and children
Inclusion criteria:	• Less than 16 years and >38 weeks corrected gestational age • Emergency referrals accepted to a participating Paediatric Intensive Care Unit (PICU) requiring mechanical ventilation within first 6 hours of face-to-face contact with PICU or transport team • Receiving supplemental oxygen for abnormal gas exchange
Exclusion criteria	• Death perceived as imminent • 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 or • Known or suspected uncorrected congenital cardiac disease • End-of-life care plan in place with limitation of resuscitation • Recruited to Oxy-PICU in previous admission
Anticipated duration of recruitment:	6 months
Duration of participant follow-up:	PICU discharge
Definition of end of trial:	Last participant, last follow-up

Figure 1 Trial schema



2.0 Background

The optimal targets for systemic oxygenation in paediatric critical illness are unknown. Intensive care staff prevent severe hypoxia wherever possible but beyond this there is no consensus. Practice varies widely with age, diagnosis and treating doctor.[1, 2] This uncertainty about the optimal oxygenation target is illustrated by the variance in national guidelines in even the most common cause of acute infant respiratory distress: respiratory syncytial virus bronchiolitis. The US American Academy of Pediatrics recommends a peripheral oxygen saturation (SpO_2) target >90%[3] whereas the Scottish Intercollegiate Guidelines Network recommend $SpO_2 \geq 94\%$.

Oxygenation targets have become a 'hot topic' for clinical trials because of observational data indicating that *high* levels of arterial oxygenation are associated with poor outcomes in resuscitation of the newborn, adult critical illness, myocardial infarction, post-cardiac arrest and possibly also in respiratory failure.[4] When added to the known risks of severe hypoxia, a 'U-shaped' relationship between arterial oxygenation and risk of death emerges.[5, 6] We have recently completed a systematic review of the paediatric literature and although the data are scarce, the same pattern of increased risk and both high and low levels of arterial oxygenation has been observed.[7]

Our recent cohort study of 7410 critically ill children from GOSH is a significant addition to this literature.[7] In this population we have demonstrated exactly such a 'U-shaped' relationship between admission arterial oxygen tension and survival. This pattern persists after adjustment for case-mix (including congenital cyanotic heart disease) and other indicators of physiological severity.

This complex relationship between oxygenation and outcome may reflect the balance between harm from hypoxia at one end, and a combination of increased oxygen free radical damage and iatrogenic injury from more aggressive treatments at the other.[6]

As part of the UCL/ Southampton 'Xtreme Everest' and 'Xtreme Everest 2" (XE2) collaborations (http://www.xtreme-everest.co.uk) we have an established interest in the genetic and physiological adaptations to hypoxia and its relevance to critical illness.[8, 9] A key observation is that any risk of hypoxia is *very* context dependent.[6]

Our lack of knowledge of the safest oxygen level for a critically ill child matters. Around 19,000 such children are admitted to PICUs in the UK annually. Around 75% of these receive artificial support for ventilation in some form. The primary aim of this artificial ventilation is to support blood oxygen at a safe level. But since this optimal level is unknown, clinicians typically default to targeting physiologically normal or even supranormal values. With other parameters during critical illness, this approach of '*normalisation of physiology*' is known to be either harmful or of no benefit.[10-13] In neonatal and adult intensive care patients the choice of oxygen targets are known to influence survival rates, lengths of stay and costs. Three large randomized studies in extreme preterm infants compared lower (85-89%) with higher targets (91-95%).[14] Unexpectedly, an increased risk of death (1.45; 95% confidence interval [CI], 1.15 to 1.84; p=0.002) was seen with the lower oxygen targets. In contrast, very recent pilot data in adult critical illness demonstrate a trend toward the *opposite* effect: i.e. reduced mortality with lower oxygenation targets in the sickest patients: relative risk 0.49 (95%CI: 0.20-1.17; p=0.10).[15] Similarly, harmful effects of supplemental oxygen have been demonstrated in adults with ST elevation myocardial infarction.[16, 17] In October 2016 the single centre Oxy-ICU study[18] in adults was stopped early because of a significant survival advantage (absolute risk reduction for ICU mortality of 8.6% (95%CI 1.7-15% p=0.01) in the conservative oxygenation group). Even prior to these data there has been a move in adult intensive care is a move towards to lower oxygen targets e.g. SpO_2 88-95%.[4]

The only paediatric trial data – in non-critically ill children with bronchiolitis – demonstrate equivalent safety of a peripheral oxygen saturation (Sp02) target of $\geq$90% when compared to $\geq$94%. Later hospital discharges were seen with the higher target (ratio of length of stay 1.28, 95% CI 1.09-1.50, p=0·003).[19]

Current practice favours very generous oxygen targets. We have conducted an analysis of around 5 million $Sp0_2$ values averaged over for 5 seconds in December 2015 on GOSH PICU. 30% of recorded values were 100% and >60% were $\geq$95%.[20]

We believe that there is an urgent need for high quality clinical evidence to inform on the optimal targets of systemic oxygenation during paediatric critical illness. Inferences 'up' from extremely premature infants or 'down' from adults are in conflict and unlikely to be valid in children because of age-related differences in the acute physiological responses to hypoxia/hyperoxia and distinct co-morbidities.

A clinical trial comparing current (liberal) targets for systemic oxygenation with lower (conservative) targets in critically ill children is therefore required. This pilot study is a crucial step to understand if this is possible and also affords the opportunity to learn more about the biological mechanisms underlying costs and benefits of oxygen therapy in children.

3.0 Aim and objectives

3.1 Aim

The overall aim of this study is to determine if it is possible to perform a safe, adequately powered, and affordable multicentre study in critically ill children comparing current practice of liberal targets for systemic oxygen levels with more conservative targets.

The underlying hypothesis is that the harm of interventions to raise arterial oxygen saturation to >94% exceeds the benefits of these interventions.

3.2 Objectives

1) To test the willingness of clinicians to screen, recruit and randomise eligible patients
2) To estimate the recruitment rate
3) To test, following randomisation, delivery of, and adherence to, the intervention and demonstrate separation between the groups
4) To test acceptability of the deferred consenting procedures and participant information
5) To test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event (AE) reporting
6) To inform final selection of a patient-centred primary outcome measure
7) To estimate the characteristics (e.g. standard deviation) of the selected patient-centred primary outcome measure to inform sample size estimation
8) To inform content and time needed for final data collection
9) To investigate the impact of conservative and liberal oxygenation strategies on biomarkers of ischaemic / oxidative injury and antioxidant status.

4.0 Trial Design

4.1 Design

Oxy-PICU is a pragmatic, open, pilot randomised controlled trial in infants and children accepted for emergency admission to a participating PICU.

4.2 Setting

Three PICUs representing typical configurations for UK PICUs (general or combined ICUs in general academic medical centres or within stand-alone children's hospitals).

The study sites are:

- Great Ormond Street Hospital for Children
    - *Transport Team: Children's Acute Transport Service (CATS)*
- St Mary's Hospital
    - *Transport Team: Children's Acute Transport Service (CATS)*
- Southampton General Hospital
    - *Transport Team: Southampton Oxford Retrieval Team (SORT)*

4.3 Study sites

In this protocol, 'site' refers to any hospital where the Oxy-PICU Pilot Study is conducted. Sites must be able to comply with:

- all responsibilities as stated in the Oxy-PICU Clinical Trial Site Agreement;
- the study treatments, follow-up schedules and all requirements of the study Protocol;
- the Research Governance Framework or Policy Framework for Health and Social Care Research (as applicable);
- data collection requirements; and
- International Conference on Harmonisation guidelines on Good Clinical Practice (ICH-GCP).

Site requirements

Sites must:

- identify and sign-up a local appropriate Principal Investigator (PI);
- identify a responsible Oxy-PICU Research Nurse (to be funded centrally);
- 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, where possible, to recruit all eligible patients to Oxy-PICU and to maintain a screening log.

Site initiation and activation

Site initiations will be performed through site initiation meetings held at each individual site.

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

- all relevant institutional approvals (e.g. confirmation of capacity and capability);
- a fully signed Oxy-PICU Clinical Trial Site Agreement; and
- Delegation Log.

Once the ICNARC CTU have confirmed that all documentation is in place, a site activation email will be issued to the 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 version of the Protocol;
- all relevant site staff are trained in the protocol requirements;
- all study staff are trained appropriately, e.g. GCP;
- appropriate recruitment and care for patients in the study;
- timely data entry; and
- prompt notification of all AEs (as specified in Section 5).

The PIs, other investigators and all local staff involved in the conduct of the study at the site must be authorised on the Oxy-PICU Delegation Log, held at site, and copied to the ICNARC CTU when any changes are made.

5.0 Outcome Measures

5.1 Primary

Number of eligible patients recruited per site per month

5.2 Secondary

- Proportion of parents/legal representatives refusing deferred consent
- Proportion of eligible patients randomised (target 50%)
- Distribution of time to randomisation
- Proportion of systemic oxygen saturations within the target range in each group
- Proportion of patients in each arm requiring other treatments influencing tissue oxygen delivery (blood transfusion, inotropic support)
- Characteristics and completeness of potential primary endpoints for a definitive study including: length of ventilation, length of PICU stay, PICU mortality, hospital mortality, days of organ specific support
- Observed AEs
- Time taken for data collection and entry
- Distribution of markers of ischaemia and antioxidant status

6.0 Trial Population

Infants and children receiving treatment at a participating site who fulfil all of the inclusion criteria and none of the exclusion criteria below.

6.1 Inclusion criteria

- Less than 16 years and more than 38 weeks corrected gestational age
- Emergency admission accepted to a PICU requiring mechanical ventilation within first 6 hours of face-to-face contact with PICU staff or transport team
- Receiving supplemental oxygen for abnormal gas exchange

6.2 Exclusion criteria

- Death perceived as imminent
- 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
- Recruited to Oxy-PICU in a previous admission

Potentially eligible infants and children will be screened against the inclusion/exclusion criteria by transport team and PICU staff supported by the Oxy-PICU trial team. Randomisation will follow a 'research without prior consent' model and parents/guardians will be approached to discuss participation in Oxy-PICU as soon as is reasonably practical, but within 48 hours.

Infants and children who are eligible (fulfil all of the inclusion criteria and none of the exclusion criteria) but not randomised, or who fulfil all of the inclusion criteria but meet one or more of the exclusion criteria, will be recorded in the Oxy-PICU screening log.

6.3 Co-enrolment

The Trial Management Group (TMG) 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.

7.0 Pre-randomisation care

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

8.0 Consent Procedures

8.1 Consent prior to hospital discharge

Patients receiving mechanical support to ventilation requiring supplemental oxygen will most often need this treatment started in a life-threatening emergency, where any delay in commencing treatment will be detrimental.

This will make any attempt to obtain fully informed consent from parents/legal representatives during an emergency inappropriate, and cause additional stress to families who are already distressed by their child's illness. Therefore, 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 applied as soon as possible. This method is known as 'deferred' or 'retrospective' consent and which is recognised in European Law.[21] The consenting process is based on previous work and studies in this area.[22-24]

NB. The Oxy-PICU study team recognises that the use of the terms 'deferred' and 'retrospective' are misnomers as a child will have already received an intervention as part of the study before any information is given or consent is sought. Rather, the process should be understood, first, as the provision of information about what has already happened, and then as an invitation to consent for future procedures (where appropriate) and permission for the use of any data already collected.

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

A Participant Information Sheet (PIS) for parents/legal representatives 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 consequences 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 representatives 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, the doctor or nurse will invite the parent/legal representative to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/legal representative, a copy placed in the child's medical notes and the original kept in the Investigator Site File. The child's GP will be sent a letter to inform them of the child's participation in the study, provided consent has been given for this.

Due to 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 (e.g. they regain capacity). 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. In all other respects, the assenting procedures will follow the consenting procedures as described above. 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.

8.2 Death prior to consent being sought

In a 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 representatives of the involvement in the research study. Deferred consent can be sought from parents/legal representatives 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 representatives (B-PIS) and Consent Form (bereaved) would be used.

If deferred consent is not sought prior to the parents'/legal representatives' departure from the hospital, then the parents/legal representatives will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the B-PIS and Consent Form (bereaved)() by post 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 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 B-PIS and Consent Form (bereaved)) will be sent to the bereaved family. This second letter will provide the same information as the first letter. In addition, 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 however all samples taken will be destroyed unless the family notify the site research team otherwise.

8.3 Discharge prior to consent being sought

In the unlikely situation where a participant is discharged from hospital before consent has been sought, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal representatives 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 representatives 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. In addition, 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.

8.4 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 state 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 Non-consent/Withdrawal of Consent Form should be completed and added onto the secure data entry

system. 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).

In the case of non-consent / withdrawal from the study, any samples collected will be destroyed.

8.5 Consent questionnaire

For parents/legal representatives who are approached for consent in person, as part of the PIS, parents/legal representatives will be provided with information about the option to complete a questionnaire regarding their views on the consenting procedures for the Oxy-PICU Pilot Study.

Following the consent discussion (see Section 8.1) one of the hospital's local Oxy-PICU team (a member of the healthcare team) will give a copy of the Oxy-PICU Pilot Study Consent Questionnaire to each parent/legal representative to complete. The questionnaire will be placed in a stamped self-addressed envelope and returned by post to the ICNARC CTU Oxy-PICU trial team. This will only be offered to parents/legal representatives who are approached for consent in person.

Any questionnaires highlighting specific concerns related to the conduct of hospital staff will be fedback to the site PI to investigate further and act upon as required. Any other areas of concern (eg. coercion by a family member) will be used to inform future research design.

9.0 Randomisation

Randomisation must occur as soon as eligibility has been confirmed with the aim of commencing treatment as soon as possible within the first 6 hours of the infant or child being in face-to-face contact with the PICU or Transport Staff.

Participants will be randomly allocated (1:1) to either the conservation (88-92%) or liberal (>94%) oxygen target group by a computer generated dynamic procedure (minimisation) with a random component. Minimisation will be performed on age (<12 months / ≥12 months); on site (GOSH/SMH/SGH); on primary reason for admission (lower respiratory tract infection vs. Other) and on 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. To randomise a participant, an authorised staff member will log onto a secure web-based randomisation system and enter the participant's details to obtain a unique four-digit trial number and allocation to one of the two treatment groups.

In the event of any issues with eligibility or randomisation, one of the clinical members of the Trial Management Group (TMG) will be available 24 hours/seven days per week to address any emergency recruitment/randomisation issues.

Emergency 24/7 telephone number: *<<TO BE INSERTED>>*

Following screening and randomisation, the Oxy-PICU Case Report Form (CRF), will be made available to the clinical team. An Oxy-PICU Trial Number and treatment allocation will be assigned, and time of randomisation will be recorded on the Oxy-PICU CRF.

10.0 Trial treatment

10.1 Liberal group

Participants allocated to the liberal oxygenation group will receive supplemental oxygen and ventilator settings at the discretion of the treating clinical team with the aim of maintaining peripheral oxygen saturations >94%. This will be continued until all ventilator support (delivered invasively or non-invasively) has been discontinued during this PICU admission.

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

10.2 Conservative group

Participants allocated to the conservative group will receive supplemental oxygen and ventilator settings at the discretion of the treating clinical team with the aim of maintaining peripheral oxygen saturations between 88% and 92% (inclusive). This will be continued until all ventilator support (delivered invasively or non-invasively) has been discontinued during this PICU admission.

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

11.0 Assessments

11.1 Data collection

Detailed guidance for the collection of data will be provided in the trial-specific Standard Operating Procedure (SOP). All data items will be objectively defined according to relevant national and international guidelines.

11.2 Time points for data collection

- Baseline/randomisation;
- Daily during PICU admission; and
- At discharge from the PICU (where relevant) and hospital.

11.3 Data collected at baseline/randomisation

The following data are required for risk adjustment and stratification:

- Age;
- Gender;
- Acute diagnosis;
- Any chronic diagnosis;
- Severity of gas exchange;
- Suspected cause of acute respiratory failure;
- Weight; and
- PIM2r score.

11.4 Data collected daily during PICU admission

- Ventilator mode including mean airway pressure and FiO_2
- Interventions for organ support: including use of vasoactive drugs, ECMO, blood transfusion, renal support and neuromuscular blocker or sedative drug infusions
- SpO_2 values will be extracted from electronic charting systems at a minimum of hourly (for ICIP systems) or each 5 seconds where the high resolution data extraction and storage systems are available (currently only GOSH)

11.5 Data collected at discharge from PICU

- Date of discharge;
- Survival status; and
- Discharge diagnosis.

11.6 Sample collection to assess possible mechanisms of oxidative injury

Blood from indwelling invasive lines will be sampled on within 24 hours of randomisation and again up to 72 hours post-randomisation (or immediately prior to removal of suitable invasive sampling lines in patients with an anticipated shorter length of stay). Plasma from samples of 1-1.5 mls of whole blood will be analysed for malondialdehyde, ischemia-modified albumin, and total antioxidant status. Peripheral blood mononuclear cells hypoxia-inducible factor- 1 alpha mRNA expression will also be estimated. Other markers of plasma and PBMC oxidative stress may be investigated. Urine samples will also be taken at the same time points (within 24 hours and up to 72 hours post-randomization) to investigate markers of oxidative stress.

All samples will be taken in a way to minimise burden for the patient and will be collected alongside routine clinical samples usually taken in a PICU and will not interfere with provision of any ongoing care. Blood samples will be stored at the local hospital in which the patient was admitted in -20^{O}C freezers and collected by clinical research fellows monthly and transferred on dry ice to -80^{O}C freezers at University College London Great Ormond Street Institute of Child Health (UCL GOS ICH) where the analysis will take place.

12.0 Follow-up

Patients will be follow-up until discharge from a participating PICU.

13.0 Data management guidelines

13.1 Case Report Forms and data entry

All participant data collected will be entered onto paper Case Report Forms (CRFs) prior to entry onto a secure web-based data entry system. The Site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated by the Site PI to qualified members of the research team and should be recorded on the Delegation Log.

No patient identifiable date will be collected centrally during the course of the Oxy-PICU Pilot Trial.

During the conduct of the trial, all electronic participant data will be encrypted and all trial documents stored securely at the site or the ICNARC CTU, as appropriate. On completion of the trial, all participant data (electronic and paper) and other trial documents will be archived securely and retained for fifteen years at the site, the sponsor or at the ICNARC CTU, as appropriate (see section 16.0).

ICNARC is registered under the Data Protection Act 1998 and all ICNARC CTU staff have undergone data protection and ICH GCP training.

13.2 Data validation

Data entered onto the secure trial database will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the research team at participating sites for resolution.

14.0 Adverse events

The following definitions have been adapted from Directive 2001/20/EC, of 4 April 2001, of the European Parliament (Clinical Trials Directive) and ICH GCP E6 guidelines:

14.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence or effect in a participant treated on a trial protocol, which does not necessarily have a causal relationship with trial treatment. An AE can therefore be any unfavourable symptom or disease temporally associated with the use of the trial treatment, whether or not it is related to the trial treatment.

14.2 Serious adverse event

- A serious adverse event (SAE) is defined as an AE that:
- results in death;
- is life threatening (the term “life-threatening” 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);
- requires in-patient hospitalisation or prolongs existing hospitalisation;
- results in persistent or significant disability/incapacity;
- consists of a congenital anomaly or birth defect.

14.3 Recording and reporting procedures

All infants and children eligible for Oxy-PICU are critically ill and due to the complexity of their condition are at increased risk of experiencing AEs. Many of these events are expected as a result of the

infant/child's medical condition and standard treatment received in the PICU, but may not be related to participation in the trial. Consequently, any AEs occurring as a result of the infant/child's medical condition or standard critical care treatment will not be reported. Pre-existing conditions do not qualify as AEs unless they worsen, but should be documented in the infant/child's medical notes.

AEs that occur between randomisation and PICU discharge must be recorded in the participant's medical notes and on the Oxy-PICU CRF. Information regarding date and time of event onset, severity and relatedness of the AE to trial treatment must be recorded (definitions below).

Those meeting the definition of a SAE (i.e. severity 3, 4 or 5 – see section 14.4) must, in addition, be recorded in the SAE Log and reported to the ICNARC CTU, using the trial specific Oxy-PICU SAE Reporting Form, by fax within **24 hours** of observing or learning of the SAE. All sections of the SAE Reporting Form must be completed.

The process for recording and reporting AEs and SAEs is summarised in Figure 2.

14.4 Severity

The Site PI, or other delegated investigator(s) (recorded in the Delegation of Trial Duties Log), must perform an assessment of severity for each AE using the following criteria:

0. **None**: indicates no event or complication.
1. **Mild**: complication results in only temporary harm and does not require clinical treatment.
2. **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.
3. **Severe**: complication requires clinical treatment and results in significant prolongation of hospital stay, permanent functional limitation.
4. **Life-threatening**: complication that may lead to death.
5. **Fatal**: indicates that the participant died as a direct result of the complication/adverse event.

14.5 Relatedness

The Site PI or other delegated investigator(s) must perform an assessment of relatedness for each AE. This must be determined as follows:

- **None**
  There is no evidence of any relationship.
- **Unlikely**
  There is little evidence to suggest a 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).
- **Possible**
  There is some evidence to suggest a 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).
- **Probable**
  There is evidence to suggest a relationship and the influence of other factors is unlikely.
- **Definitely**
  There is clear evidence to suggest a relationship and other possible contributing factors can be ruled out.

14.6 Expectedness

The Site PI or other delegated investigator(s) must perform an assessment of expectedness for each AE regardless of its relationship to the trial procedures. This assessment must be performed using the list of expected AEs in Appendix 2 and determined as follows:

- **Expected**
  The event is listed as an expected AE in Appendix 2, or is considered by the investigator to be an expected complication in this patient population (this would include rare complications).

- **Unexpected**
  The event is not listed as an expected AE in Appendix 2, or is considered by the investigator to be an unexpected event.

14.7 Follow-up of serious adverse events

All SAEs must be followed-up until resolution. The Site PI or other delegated investigator(s) must provide follow-up SAE report(s) if the SAE has not been resolved at the time of the initial report submission.

14.8 Central processing of serious adverse event reports

On receipt of the SAE report, a clinical member of the Oxy-PICU Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not 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 Chief Investigator, TMG, Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) for review on a regular basis (as deemed necessary).

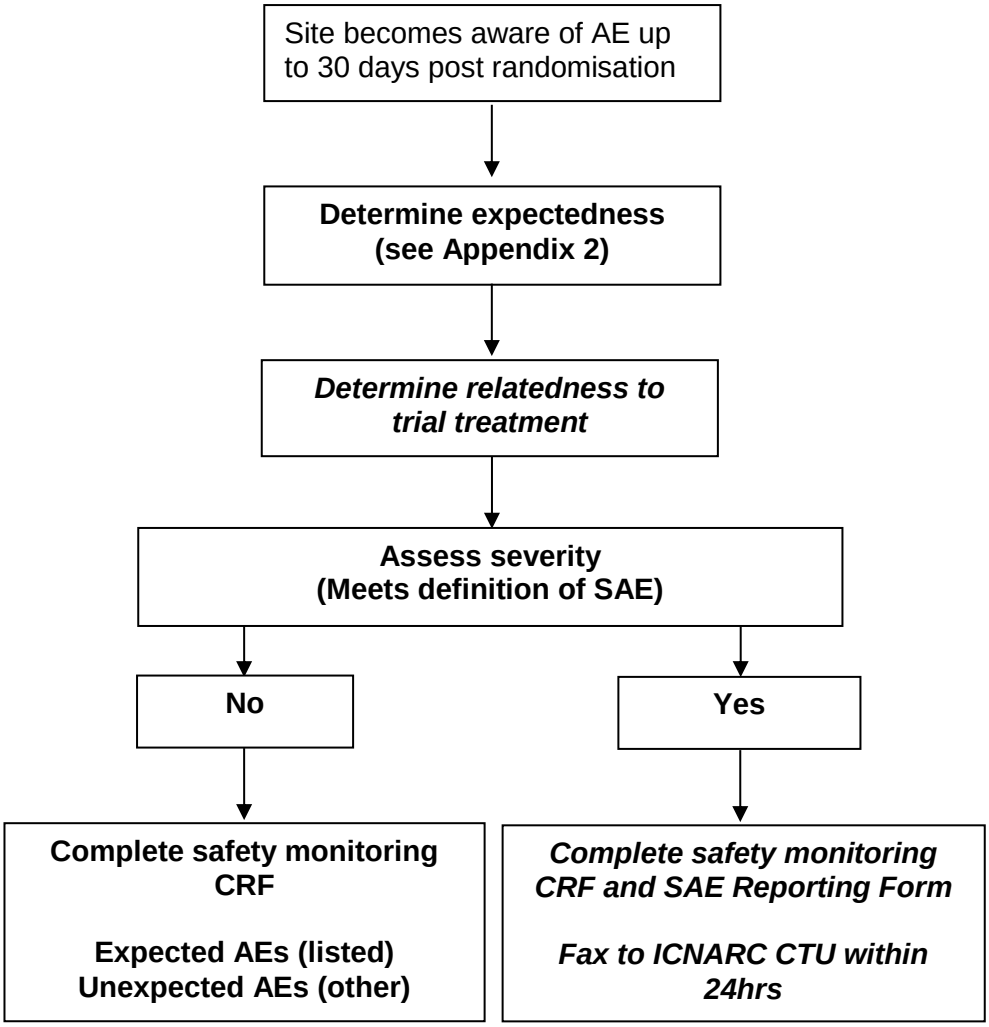
14.9 Additional safety monitoring

The ICNARC CTU will also monitor data for documented AEs that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in AEs, the TMG will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the ICNARC CTU will inform the REC as appropriate.

14.10 Notifying the Research Ethics Committee

AEs leading to treatment failure will be reported in the annual progress report which will be submitted by the ICNARC CTU to the REC annually. This will commence one year from the date of approval for the trial.

Figure 2 Adverse event recording and reporting



15.0 Trial monitoring and oversight

The ICNARC CTU will conduct at least one monitoring visit to participating sites during the course of the pilot trial. In addition, the REC may request access to source data/documents for audit and review. Trial participants and their parents will be informed of this during the informed consent process (see section 8.0).

Following a routine monitoring visit, a report will be sent, which will summarise the visit and the documents reviewed, along with any findings. The Site PI will be responsible for ensuring that all findings are addressed appropriately.

Additional site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance with the Oxy-PICU Pilot Trial Protocol.

16.0 Trial closure

16.1 End of trial

The end of the trial will be when the last participant has completed their PICU admission.

16.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will archive securely all centrally-held trial-related documents for a minimum fifteen 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 fifteen 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, held centrally and locally, should be available for inspection by appropriate authorities upon request.

16.3 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 Pilot Study Protocol.

17.0 Trial management and oversight committees

17.1 Good research practice

Oxy-PICU will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures, based on these MRC 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.

17.2 Trial Management Group

All day-to-day management of Oxy-PICU will be the responsibility of the TMG. Members of the TMG will include the Oxy-PICU Trial Coordinator, the Chief Investigator and the clinical co-investigators. The TMG will meet regularly to discuss management and progress of the trial and findings from other related research.

17.3 Trial Steering Committee

The trial will be supervised by the Trial Steering Committee (TSC), which will be chaired by an independent member Professor Robert Tasker. The TSC will include at least two additional independent members and a service user representative.

17.4 Data Monitoring and Ethics Committee

The Data Monitoring and Ethics Committee (DMEC) will be chaired by Peter Davis. All members of the DMEC will be independent of both the Oxy-PICU TMG and the TSC. The DMEC will operate under the DAMOCLES Charter[19-20], 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.

17.5 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.

18.0 Statistics

18.1 Sample size calculation

The Oxy-PICU Pilot Study is set up to test the feasibility of the protocol to recruit eligible patients. Therefore there is no primary outcome to be compared between the two groups and, hence, a usual power calculation to determine sample size is not appropriate. Instead, the sample size has been determined to be adequate to estimate critical parameters to be tested to a necessary degree of precision.

Based on available data from PICANet, it is anticipated that the participating sites will recruit approximately 4-10 children per month, providing a total of approximately 120 children in 6 months.

Recent research has demonstrated that a standard sample size for a pilot study (approximately 30 patients) will result in an imprecise estimate of the standard deviation of a potential outcome measure which will frequently lead to definitive studies that are either underpowered (if the imprecision of the estimated SD is not taken into account in the sample size calculation) or inefficient (if it is).[25] Sim and Lewis recommend a sample size of around 60 patients would usually be sufficient to estimate the SD for a continuous outcome measure; however, they note that estimating the precision of a binary outcome will require a larger sample size, typically requiring between 98 and 260 patients.[26] For example, one potential outcome measure for Oxy-PICU is 30-day all-cause mortality, which is anticipated to be in the region of between 5-8% (estimate from PICANet data). The proposed sample size of 120 patients for Oxy-PICU would enable the mortality to be calculated with a precision of approximately +/- 5%.

18.2 Statistical analysis

Descriptive analysis will be conducted to assess the objectives of Oxy-PICU.

19.0 Ethical compliance

The Oxy-PICU Pilot Study will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as the ICNARC CTU's research policies and procedures (see section 18.0).

The trial has received Health Research Authority approval on 06/01/2017 including a favourable opinion from South Central - Berkshire research ethics committee (REC). The ICNARC CTU will submit annual progress reports and all amendments to the Oxy-PICU Pilot Study Protocol to the REC for review. The ICNARC CTU will provide relevant approved trial documents and other related materials to participating sites.

It is the responsibility of the Site PI to obtain the necessary local approvals for the Oxy-PICU Pilot Study, including confirmation of capacity and capability from the Trust Research & Development (R&D) Department. The Site PI should submit the site information pack, which will include: current approved version of the Protocol, PIS; Consent Form; and any other written information to be given to participants, to the R&D Department. It is also the responsibility of the Site PI to inform the R&D Department of any subsequent revisions to the Protocol or other trial documents. Evidence of NHS Trust R&D confirmation of capacity and capability must be provided to the ICNARC CTU prior to recruitment of participants.

19.1 Participant confidentiality and data protection

No identifiable participant data will be required by the ICNARC CTU, as all follow-up data will be collected at participating sites. All participant data will be stored securely.

ICNARC is registered under the Data Protection Act (1998) and all ICNARC CTU staff have undergone data protection and ICH GCP training.

20.0 Sponsorship and Indemnity

20.1 Sponsor details

Sponsor Name:	Great Ormond Street Hospital for Children NHS Foundation Trust
Address:	Great Ormond Street Hospital for Children NHS Foundation Trust Great Ormond Street London, WC1N 3JH
Contact:	Emma Pendleton
Email:	research.governance@gosh.nhs.uk

20.2 Indemnity

University College London holds Professional Indemnity insurance (Policy number B1262 F10153316, Arthur J Gallagher) meets the potential legal liability of the Sponsor (GOSH) and employees for harm to participants arising from the design of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct and management of the research is provided by the NHS indemnity scheme or through professional indemnity.

21.0 Funding

Oxy-PICU is funded by Great Ormond Street Hospital Children's Charity, Registered Charity No. 235825.

22.0 Publication policy

The final report, including a detailed description of the trial, results and recommendations for future policy and practice and future research, will be submitted to the Great Ormond Street Hospital Children's Charity. Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals. All participant data will be anonymised before publication.

References

1. Raman S, Ray S, Peters MJ. Survey of Oxygen Delivery Practices in UK Paediatric Intensive Care Units. Crit Care Res Pract. 2016;2016:6312970.

2. Helmerhorst HJ, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Jonge E, et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. Ann Intensive Care. 2014;4:23.

3. Ralston SL, Lieberthal AS, Meissner HC. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. Pediatrics. 2014;134(5):e1474-e1502. Pediatrics. 2015;136(4):782.

4. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. Ann Intensive Care. 2015;5(1):42.

5. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12(6):R156.

6. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med. 2013;41(2):423-32.

7. Raman S, Prince NJ, Hoskote A, Ray S, Peters MJ. Admission PaO2 and Mortality in Critically Ill Children: A Cohort Study and Systematic Review. Pediatr Crit Care Med. 2016;17(10):e444-e50.

8. Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in climbers on Mount Everest. N Engl J Med. 2009;360(2):140-9.

9. Scrase E, Laverty A, Gavlak JC, Sonnappa S, Levett DZ, Martin D, et al. The Young Everest Study: effects of hypoxia at high altitude on cardiorespiratory function and general well-being in healthy children. Arch Dis Child. 2009;94(8):621-6.

10. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301-8.

11. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007;356(16):1609-19.

12. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999;341(11):785-92.

13. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.

14. Tarnow-Mordi W, Stenson B, Kirby A, Juszczak E, Donoghoe M, Deshpande S, et al. Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants. N Engl J Med. 2016;374(8):749-60.

15. Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. Am J Respir Crit Care Med. 2016;193(1):43-51.

16. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation. 2015;131(24):2143-50.

17. Khoshnood A, Carlsson M, Akbarzadeh M, Bhiladvala P, Roijer A, Bodetoft S, et al. The Effects of Oxygen Therapy on Myocardial Salvage in ST Elevation Myocardial Infarction

Treated with Acute Percutaneous Coronary Intervention: The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) Study. Cardiology. 2015;132(1):16-21.

18. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA. 2016;316(15):1583-9.

19. Cunningham S, Rodriguez A, Boyd KA, McIntosh E, Lewis SC. Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. Health Technol Assess. 2015;19(71):i-xxiii, 1-172.

20. Ray SR, E. Raman, S. Peters, M. Liberal oxygenation in paediatric intensive care: retrospective analysis of high resolution SpO2 data. Intensive Care Medicine.Under review.

21. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. [cited 2016 12 October]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32014R0536.

22. Woolfall K, Frith L, Dawson A, Gamble C, Lyttle MD, Young B. Fifteen-minute consultation: an evidence-based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials. Arch Dis Child Educ Pract Ed. 2016;101(1):49-53.

23. Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. BMJ Open. 2015;5(9):e008522.

24. Woolfall K, Young B, Frith L, Appleton R, Iyer A, Messahel S, et al. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. BMJ Open. 2014;4(5):e005045.

25. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004;10(2):307-12.

26. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol. 2012;65(3):301-8.

Appendix 1 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Appendix 2: Expected adverse events

Severe lactic acidosis (>5mmol/L) without otherwise known cause

Cardiac ischaemia without otherwise known cause

Acute kidney injury without otherwise known cause

Seizures without otherwise known cause

[This list is not exhaustive. If an adverse event, as defined in section 14.1, occurs this should be recorded and reported as described in section 14.0]