



Evaluating the clinical and cost-effectiveness of a conservative approach to oxygen therapy for invasively ventilated adults in intensive care.

STUDY SHORT TITLE

Intensive Care Unit **R**andomised Trial Comparing Two Approaches to **O**Xygen Therapy (**UK-ROX**).

FUNDED BY

NIHR | National Institute
for Health Research

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number: NIHR130508). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA Programme, NIHR, NHS or the Department of Health.

Reference numbers

Protocol version number and date

Version 1.54, ~~12-17 April~~ February 2022

IRAS Number

288506

REC Number

20/SC/0423

NIHR Portfolio CPMS ID

46926

ISRCTN Registry Number

ISRCTN13384956

Sponsor name and reference

Intensive Care National Audit & Research Centre (ICNARC) (reference: 01/10/20)

Funder name and reference

National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project number: NIHR130508)

Chief Investigator(s)

Professor Daniel Martin, OBE

Mr Paul Mouncey

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.

For and on behalf of the Trial Sponsor:

Signature:



Date:

12~~47~~/04~~2~~/2022

Name:

Ms Keji Dalemo,
Clinical Trials Unit Manager

Chief Investigator:

Signature:



Date:

12~~47~~/04~~2~~/2022

Name:

Professor Daniel Martin, OBE,
Professor of Perioperative and Intensive Care Medicine

UK-ROX contacts

Chief Investigator(s)	<p>Professor Daniel Martin, Professor of Perioperative and Intensive Care Medicine Peninsula Medical School University of Plymouth John Bull Building Derriford Plymouth PL6 8BU United Kingdom Tel: 07801444428 Email: daniel.martin@plymouth.ac.uk</p> <p>Mr Paul Mouncey, Head of Research ICNARC CTU Napier House 24 High Holborn London WC1V 6AZ United Kingdom Tel: 020 7269 9277 Email: paul.mouncey@icnarc.org</p>
Clinical Trials Unit	<p>Mr Alvin Richards-Belle, Trial Manager ICNARC CTU Napier House 24 High Holborn London WC1V 6AZ United Kingdom Tel: 020 7269 9277 Email: uk-rox@icnarc.org</p>
Sponsor	<p>Ms Keji Dalemo, CTU Manager ICNARC Napier House 24 High Holborn London WC1V 6AZ Tel: 020 7831 6878 Fax: 020 7831 6879 Email: ctu@icnarc.org</p>
Funder	<p>National Institute for Health Research Health Technology Assessment Programme Tel: 02380 595 656 Email: htaas@southampton.ac.uk</p>

UK-ROX Investigators

Name	Department	Organisation
Professor Daniel Martin	Medical School	University of Plymouth
Mr Paul Mouncey	Clinical Trials Unit	ICNARC
Mrs Miriam Davey	Intensive Care Unit	Maidstone and Tunbridge Wells NHS Trust
Dr James Doidge	Clinical Trials Unit	ICNARC
Dr Roger Garrett	N/A	Patient and Public Involvement (PPI) representative
Dr Doug Gould	Clinical Trials Unit	ICNARC
Professor Mike Grocott	Medicine	University of Southampton
Professor David Harrison	Clinical Trials Unit	ICNARC
Mrs Joanne Jones	Intensive Care Unit	Maidstone and Tunbridge Wells NHS Trust
Dr Ronan O'Driscoll	Respiratory Medicine	Salford Royal NHS Foundation Trust
Mr Alvin Richards-Belle	Clinical Trials Unit	ICNARC
Professor Kathy Rowan	Clinical Trials Unit	ICNARC
Dr Zia Sadique	Health Services Research and Policy	London School of Hygiene and Tropical Medicine
Dr Paul Young	Intensive Care Unit	Wellington Regional Hospital

Summary

Data category	Information
Public title	Intensive Care Unit Randomised Trial Comparing Two Approaches to OXYgen Therapy (UK-ROX)
Scientific title	Evaluating the clinical and cost-effectiveness of a conservative approach to oxygen therapy for invasively ventilated adults in intensive care
Primary registry and trial identifying number	ISRCTN13384956
Date of registration in primary registry	8 December 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 (ICNARC)
Contact for public queries	Mr Alvin Richards-Belle Tel: 020 7269 9277 Email: UK-ROX@icnarc.org
Contact for scientific queries	Professor Daniel Martin Tel: 07801 444428 Email: daniel.martin@plymouth.ac.uk
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Mechanical ventilation (MV) with supplementary oxygen
Intervention(s)	Conservative oxygen therapy vs. usual oxygen therapy
Inclusion and exclusion criteria	<p>Ages eligible for study: Adult (aged ≥ 18 years)</p> <p>Sexes eligible for study: both</p> <p>Accepts healthy volunteers: no</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Aged ≥ 18 years 2. Receiving invasive mechanical ventilation in the ICU following an unplanned ICU admission OR invasive mechanical ventilation started in the ICU 3. Receiving supplemental oxygen (fractional inspired concentration of oxygen (FiO_2) > 0.21) at the time of enrolment <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Previously randomised into UK-ROX in the last 90 days 2. Currently receiving extracorporeal membrane oxygenation (ECMO)

Data category	Information
	3. The treating clinician considers that one trial intervention arm is either indicated or contraindicated
Study type	<p>A large-scale, multi-centre, data-enabled, registry-embedded, randomised clinical trial (RCT) with an internal pilot phase and integrated economic evaluation.</p> <p>Interventional</p> <p>Allocation: randomised Blinding: cannot be blinded Primary purpose: prevention</p>
Date of first enrolment	5 May 2021
Target sample size	16,500
Primary outcome	90-day all-cause mortality
Secondary outcomes	<ul style="list-style-type: none"> • In-hospital mortality (censored at 90 days) • Mortality at ICU discharge, 60 days and one year • Duration of ICU and acute hospital stay (censored at 90 days) • HrQoL, assessed using the EuroQol EQ-5D-5L questionnaire, at 90 days
Economic outcomes	<p>Primary economic evaluation outcomes:</p> <ul style="list-style-type: none"> • Incremental costs, QALYs and net monetary benefit at 90 days <p>Secondary economic evaluation outcomes:</p> <ul style="list-style-type: none"> • HrQoL, assessed using the EuroQol EQ-5D-5L questionnaire, at 90 days • Resource use and costs at 90 days • Estimated lifetime incremental cost-effectiveness.

Contents

Reference numbers.....	2
Signature page.....	3
UK-ROX contacts.....	4
UK-ROX Investigators.....	5
Summary.....	6
Contents.....	8
Abbreviations.....	10
1. Background and rationale.....	11
1.2 Review of existing evidence.....	11
1.3 Why is this research important to patients and the NHS.....	12
1.4 UK-ROX and Mega-ROX.....	12
1.5 Pilot and feasibility work.....	13
1.6 Data-enabled design.....	13
2. Aim and objectives.....	13
2.1 Aim.....	13
2.2 Objectives.....	13
3. Methods.....	14
3.1 Design.....	14
3.2 Setting.....	14
3.3 Population.....	15
3.4 Recruitment and consent.....	16
3.6 Interventions.....	19
3.7 Safety monitoring.....	21
3.7.2 Assessment.....	21
3.7.3 Recording and reporting procedures.....	22
3.7.4 Notifying the Research Ethics Committee.....	23
3.8 Data collection.....	25
3.9 Questionnaire follow-up.....	26
3.10 Outcomes.....	27
4. Statistics and data analysis.....	28
4.1 Sample size.....	28
4.2 Statistical analysis.....	29
5. Monitoring and auditing.....	32
5.1 Central monitoring.....	32

5.2 Site monitoring.....	32
6. Trial closure.....	32
6.1 End of trial	32
6.2 Archiving trial documents.....	32
7. Trial management and oversight.....	33
7.1 Good research practice.....	33
7.2 Trial Management Group (TMG).....	33
7.3 Trial Steering Committee (TSC)	33
7.4 Data Monitoring and Ethics Committee (DMEC)	33
8. Ethics, approvals and dissemination.....	33
8.1 Ethical compliance	33
8.2 Trial registration	34
8.4 Patient and Public Involvement (PPI)	34
8.5 Data protection and participant confidentiality	34
8.6 Declaration of interests	34
8.7 Dissemination	34
9. Sponsorship and funding	35
9.1 Sponsorship and indemnity.....	35
9.2 Funding.....	35
10. Exploring pulse oximeter Accuracy across sKin Tones (EXAKT) sub-study	35
11. References	36

Abbreviations

ABG	Arterial blood gas
AE	Adverse event
ARDS	Acute respiratory distress syndrome
ARR	Absolute risk reduction
CCMDS	Critical Care Minimum Dataset
CEA	Cost-effectiveness analysis
CI	Chief Investigator
CMP	Case Mix Programme
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring & Ethics Committee
EQ-5D-5L	European Quality of Life Scale
FiO ₂	Fractional inspired oxygen concentration
GCP	Good Clinical Practice
HrQoL	Health-related quality of life
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive care unit
INB	Incremental net benefit
MV	Mechanical ventilation
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
RRR	Relative risk reduction
SAE	Serious adverse event
SOP	Standard Operating Procedure
SpO ₂	Peripheral arterial oxygen saturation
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

1. Background and rationale

Intensive Care Unit Randomised Trial Comparing Two Approaches to OXygen Therapy (UK-ROX)

In the UK, around 184,000 people are admitted to an adult intensive care unit (ICU) each year. Over 30% (55,000) of these receive advanced respiratory support in the form of mechanical ventilation (MV) with supplemental oxygen. This makes oxygen one of the commonest drugs administered to patients in ICU. Despite this, there is insufficient evidence to guide clinicians in the use of oxygen in order to minimise the potential harm caused by giving too little or too much oxygen. The long-standing fear of harm due to hypoxia from giving too little oxygen has led to a tendency to give too much oxygen in order to counter-balance this.¹ However, too much oxygen risks damaging the lungs and other vital organs through the generation of excessive reactive oxygen species leading to oxidative stress.² Knowing the right amount of oxygen to give to increase the likelihood of patient survival and improve that quality of survival is an important clinical question.

Oxygen can be titrated from 21% (room air) up to 100% and its effectiveness can be determined by measuring a patient's peripheral arterial oxygen saturation (SpO₂). In acutely unwell patients it has been shown that giving a lower concentration of oxygen than usual, to achieve a lower than normal SpO₂ ('conservative' oxygen therapy) results in lower mortality.³ Guidance published following this suggests avoiding an SpO₂ of >96% in these acutely unwell patients.⁴ Trials have shown mixed results when comparing conservative to 'liberal' or usual oxygen therapy in patients receiving MV on an ICU,⁵⁻⁷ leaving a knowledge gap that requires urgent attention. Lacking guidance in oxygen therapy for critically ill patients means clinicians do not know the ideal SpO₂ target for patients receiving MV.

1.2 Review of existing evidence

For a number of years it has been suggested that excessive oxygen administration may harm critically ill patients.⁸ The majority of data in the intensive care literature comes from retrospective observational studies of existing databases and they provide contradictory findings.^{1, 9, 10} A substantial limitation to this approach is the assumption that survival might be related to a single or limited number of arterial blood gas (ABG) results. Another is a failure to appreciate confounding by treatment indication (i.e. more unwell patients are frequently over-oxygenated). The observational nature of these studies and small sampling window preclude any causative inferences being made. Our own study used data from 12 English ICUs and consolidated all available ABGs up to 7 days following admission to ICU. Using multivariable logistic regression, we demonstrated a strong relationship between mortality and hyperoxaemia in patients on ICU.¹¹ These data are substantiated by the combined data from ten studies of MV patients with Acute Respiratory Distress Syndrome (ARDS), which indicated that patients with high oxygen exposure were more likely to die.¹²

The evidence for conservative oxygen therapy in acutely and critically unwell adults has recently been summarised in two systematic reviews and meta-analyses, both reporting higher mortality associated with hyperoxia (RR 1.21, 95% CI 1.03 to 1.43³ and OR 1.22, 95% CI 1.12 to 1.33¹³). However, the results of the former analysis were dominated by patients in trials for myocardial infarction and stroke rather than ICU patients receiving MV.¹⁴

The largest randomised clinical trial (RCT) published to date is ICU-ROX; 1,000 MV patients were allocated to either conservative (minimal oxygen concentration required to achieve an

SpO₂ of 91-96%) or usual oxygen therapy, to evaluate the effect on ventilator-free days from randomisation until day 28.⁶ The number of ventilator-free days did not differ significantly between the conservative oxygen group and the usual oxygen group.

We extracted data from four relevant ICU RCTs (total of 1,983 patients) to produce an updated risk ratio for mortality of 0.91 (95% CI 0.75 to 1.09) indicating possible benefit in favour of conservative oxygen therapy, but with uncertainty.^{5, 6, 15, 16} These results are further complicated by the heterogenous nature of trial designs and the fact that two of the studies showing effect towards harm from liberal oxygen therapy were stopped early.^{5, 15}

The most recently published evidence in this field is a multi-centre study of patients with acute respiratory distress syndrome (ARDS) (n=205) that showed no difference in 28-day survival between the conservative and liberal oxygen therapy groups.⁷ The trial was stopped early by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two intervention groups.

These findings, taken together, demonstrate the need for a definitive, very large, multi-centre, RCT to address the question of optimal oxygenation targets in MV critically ill patients in ICU.

1.3 Why is this research important to patients and the NHS

The importance of this research is demonstrated by the large number of critically ill patients requiring MV treated in NHS ICUs each year. Of the 337,312 admissions to ICUs participating in the Case Mix Programme (CMP – national clinical audit of adult critical care) between 1 April 2017 and 31 March 2019, 96,028 (29%) received MV during their stay. Of these, 34% died before hospital discharge, extending to an anticipated 37% by 90 days. With the risk ratio from our meta-analysis of 0.91 (0.75 to 1.09) in favour of more conservative oxygen therapy, if a similar effect size is observed in UK-ROX, this would equate to >3,000 lives saved annually in the UK if the intervention was implemented. Optimising oxygen therapy may also reduce the financial burden of critical illness on society by reducing morbidity and improving quality of life after discharge.

The proportion of admissions to adult ICUs in the UK receiving MV has remained >30% over the past 10 years¹⁷ and is expected to rise with increasing admissions of elderly patients. The recent COVID-19 pandemic, in which 72% of ICU patients with COVID-19 received MV during the first epidemic wave,^{18, 19} demonstrates the need for a comprehensive evidence base for patients requiring MV as part of their ICU care. As a specialised high-cost service, it is imperative to optimise treatments that are delivered to large proportions of ICU patients.

We aim to conduct an ambitious, cost-efficient, data-enabled trial to address a fundamental knowledge gap in intensive care medicine. We will evaluate the clinical effectiveness of conservative oxygen therapy (versus usual oxygen therapy) on 90-day all-cause mortality and its cost-effectiveness for incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 90 days. We propose an RCT that will recruit 16,500 MV ICU patients into either conservative or usual oxygen therapy. We wish to provide a definitive answer as to whether reducing the amount of oxygen given to ICU patients receiving MV improves their survival and from this develop national guidance that can be easily and immediately implemented throughout the NHS.

1.4 UK-ROX and Mega-ROX

With close harmonisation, it is intended that the 16,500 patients in UK-ROX will contribute 41% of the intended patients for Mega-ROX (a global collaboration investigating oxygen therapy in critically ill patients). UK-ROX, however, is powered at 90%, as a standalone trial for the NHS, to evaluate an important absolute risk reduction of 2.5% in 90-day mortality (primary outcome). UK-ROX will collect hospital mortality as a secondary outcome (to be able to harmonise with the MEGA-ROX primary outcome) – Mega-ROX is limited to hospital mortality as its primary outcome as not all countries involved are able to link to longer-term mortality using routine data sources. These plans allow for at least a prospectively planned meta-analysis, as indicated.

1.5 Pilot and feasibility work

We have completed a feasibility RCT in the UK to assess whether it would be possible to conduct a larger national multi-centre trial to evaluate oxygenation targets in MV ICU patients in the NHS.^{20, 21} We set out to recruit 60 participants across two sites into a trial in which they were randomised to receive conservative oxygenation (SpO₂ 88-92%) or usual care (control – SpO₂ ≥96%). A total of 34 patients were recruited into the study until it was stopped due to time constraints. A number of key barriers to success were identified during the course of the study. The conservative oxygenation intervention was feasible and appeared to be safe in this small patient cohort. Our co-investigator, PY, has also completed a study of conservative versus liberal oxygen use in Australia and New Zealand (ICU-ROX).⁶ Combining lessons learnt from both of these studies, we have developed the UK-ROX and Mega-ROX protocols to definitively answer the question of which is the optimal SpO₂ target for MV ICU patients.

1.6 Data-enabled design

UK-ROX was designed to answer the research question using data-enabled, efficient methods. The trial is nested within the Case Mix Programme (CMP), a source of high quality, robust and representative data, collected from an existing network of research-active critical care units. The trial will make maximal use of routine data, with linked data from national sources forming the dataset for a high proportion of participants (only 15% will require additional primary data collection).

2. Aim and objectives

2.1 Aim

The aim of the UK-ROX trial is to evaluate the clinical and cost-effectiveness of conservative oxygen therapy for invasively ventilated adults in intensive care.

The research question is: in non-elective adults receiving mechanical ventilation and supplemental oxygen in ICU **[Population]** is conservative oxygen therapy **[Intervention]** superior to usual oxygen therapy **[Comparator]** in terms of all-cause mortality at 90 days **[Outcome]**?

2.2 Objectives

To evaluate clinical and cost effectiveness of conservative versus usual oxygen therapy on:

- 90-day all-cause mortality (primary clinical outcome)
- Incremental costs, QALYs and net monetary benefit at 90 days (primary economic outcomes)
- ICU and hospital mortality (censored at 90 days)

- Mortality at 60 days and one year
- Duration of ICU and acute hospital stay (censored at 90 days)
- Health-related quality of life (HrQoL) at 90 days

This Protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.²²

3. Methods

3.1 Design

UK-ROX is a large-scale, multi-centre, data-enabled, registry-embedded, randomised clinical trial (RCT) with an internal pilot phase and integrated economic evaluation.

3.2 Setting

3.2.1 Sites

100 adult NHS ICUs across England, Wales and Northern Ireland. General and specialist (e.g. cardiac, neuro, etc.) units will be considered, as will medical, surgical and mixed units.

3.2.2 Site requirements

- Active participation in the CMP
- Compliance with all responsibilities as stated in the UK-ROX Clinical Trial Site Agreement
- Compliance with all requirements of the trial protocol
- Compliance with the UK Policy Framework for Health and Social Care Research and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP).

3.2.3 Site responsibilities

- Identify a Principal Investigator (PI) to lead the UK-ROX trial locally
- If possible, appoint an Associate/Sub PI to assist with the running of the UK-ROX trial locally (<https://www.nihr.ac.uk/documents/associate-principal-investigator-pi-scheme/25040>)
- Identify a UK-ROX research nurse responsible for day-to-day local trial coordination
- Agree to incorporate UK-ROX into routine critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations and ensure adherence with the trial protocol
- Agree to aim to randomise all eligible patients and to maintain a Screening Log
- Agree to data collection requirements.

3.2.4 Site initiation and activation

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

- A completed site initiation visit (held in person or virtually)
- All relevant institutional approvals (e.g. local confirmation of capacity and capability)
- A fully signed UK-ROX Clinical Trial Site Agreement
- A completed Delegation Log

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation e-mail will be issued to the PIs, 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 with the most recent approved version of the trial protocol
- training of relevant site staff in accordance with the trial protocol and Good Clinical Practice (GCP) requirements
- appropriate means to identify and randomise eligible patients into the trial
- timely data collection, entry and validation; and
- prompt notification of all serious adverse events (SAEs).

All local staff (i.e. PI, Associate/Sub PI, local investigators, research teams) involved in the conduct of the trial must be trained to carry out their assigned roles. Site research staff should be signed off by the PI on the Delegation Log, once trained, and the Delegation Log copied and sent to the ICNARC CTU whenever changes are made.

Staff members solely involved in the screening and randomisation of patients should be provided with trial-specific training to carry out these tasks and recorded on the Training Log (full GCP training will not be required for these staff members).²³

3.3 Population

Adults admitted to ICUs in England, Wales and Northern Ireland who are receiving invasive MV, enrolled within 12 hours of fulfilling the below eligibility criteria.

3.3.1 Inclusion criteria

1. Aged ≥ 18 years
2. Receiving invasive mechanical ventilation in the ICU following an unplanned ICU admission (i.e. not admitted after an elective procedure) OR invasive mechanical ventilation started in the ICU (i.e. the patient was intubated in the ICU)
3. Receiving supplemental oxygen (fractional inspired concentration of oxygen (FiO_2) > 0.21) at the time of enrolment

3.3.2 Exclusion criteria

1. Previously randomised into UK-ROX in the last 90 days
2. Currently receiving extracorporeal membrane oxygenation (ECMO)
3. The treating clinician considers that one trial intervention arm is either indicated or contraindicated

3.3.3 Co-enrolment

Co-enrolment will be permitted with observational studies (including those collecting samples) without prior agreement needed.

The UK-ROX investigators will consider co-enrolment of participants onto other interventional studies where there is no possible conflict with the UK-ROX objectives. We will follow previous experience and existing guidelines from the Intensive Care Society regarding co-enrolment to other clinical trials to maximise patient involvement in research.²⁶ Co-enrolment agreements will be put in place on a case-by-case basis.

3.3.4 Screening

Potentially eligible patients admitted (or accepted for admission) to the participating ICU will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Screening Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

3.4 Recruitment and consent

3.4.1 Randomisation

Randomisation will be performed as soon as possible after confirming eligibility. Patients will be randomised 1:1 to receive conservative oxygen therapy (intervention) or usual oxygen therapy (control) using a central telephone or web-based randomisation service, available 24 hours/seven days per week. Allocation will use randomised permuted blocks of variable block sizes, stratified by site, hypoxic ischaemic encephalopathy, sepsis and acute brain pathologies (excluding hypoxic ischaemic encephalopathy).

Following randomisation into UK-ROX, each participant will be assigned a unique UK-ROX Trial Number and a CRF will be completed by the local team (*see section 3.8*).

3.4.2 Consent procedures

Patients eligible for UK-ROX become so during a period of critical illness. In non-elective patients, mechanical ventilation is an invasive procedure initiated as a life-saving measure, during an emergency clinical situation. It necessitates use of sedative and analgesic drugs (as part of standard care), leading to patients lacking mental capacity and/or the ability to communicate effectively. Moreover, the emergency clinical situation can cause profound distress for relatives, raising ethical concerns both about the burden of trying to understand the trial and the ability of a Personal Consultee (i.e. relative or close friend) to provide an opinion about trial participation during a time of great distress. For these reasons, attempts to obtain either prior informed consent from the patient, or the prior opinion of a Personal Consultee, are inappropriate.

UK-ROX will adopt a research without prior consent (RWPC) model (also referred to as 'deferred consent'), whereby eligible patients will be randomised to receive the assigned treatment as soon as possible (and no later than 12 hours after fulfilling the eligibility criteria). This is an accepted consent model in adult emergency and critical care research where participants lack mental capacity and minimises the distress and additional burden on families during a distressing time. In addition, the urgent nature of treatments delivered in ICU means that any delay to commencing treatment could be detrimental to the patient (and to the scientific validity of the trial). This consent model is covered by an Emergency Waiver of Consent under the Mental Capacity Act (approved by South Central - Oxford C Research Ethics Committee (reference: 20/SC/0423)).

In the very rare situation where a patient has been deemed by the treating clinical team to have full capacity and is able to give informed consent at the point of meeting the eligibility criteria, they will be approached directly prior to randomisation for verbal or other non-written (e.g. through blinking or hand movement) consent to take part in UK-ROX. If they provide verbal or other non-written consent, they will then be followed up for full written informed consent, in line with the procedures outlined in section 3.4.2.1. If such a participant who gave prospective verbal/non-written consent subsequently lost mental capacity, the opinion of a Personal or Nominated Consultee should be sought to advise on their continuation in the trial (see sections 3.4.2.2 and 3.4.2.3).

3.4.2.1 Patient informed deferred consent

Following randomisation, patients will be approached by a delegated member of the site research team once deemed to have full capacity to provide informed deferred consent. It is anticipated that this first approach will occur within 24-48 hours of regaining capacity. A Participant Information Sheet (PIS) will be given to the patient. The PIS will provide information about the background/rationale for the trial, what participation means for the patient (e.g. data collection, follow-up questionnaires), confidentiality and data protection and the future availability of the trial results. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in UK-ROX.

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. The Consent Form will also cover consent for access to medical records for ongoing data collection and follow-up.

After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness (i.e. someone not involved in the trial) can sign on their behalf.

In the situation where a patient is approached in hospital but wishes to have more time to consider participation, they can request to be approached via the method detailed in section 3.4.2.4.

3.4.2.2 Personal Consultee Opinion

It will usually not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into UK-ROX, a delegated member of the site research team will approach the Personal Consultee (in person or via telephone) as soon as appropriate and practically possible to discuss the trial and seek their opinion as to the patients' likely wishes and feelings regarding participating in the trial. Ideally, this approach would take place within 24-48 hours of randomisation, but once the patient's medical situation is no longer an emergency.

Where approached in person, the Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented with information on why the Personal Consultee has been approached at this stage. Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients' participation in the UK-ROX.

A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in the trial.

After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the person seeking opinion will invite the Personal Consultee to sign the Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient's medical notes and the original kept in the Investigator Site File.

If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in the trial, then the trial treatment will be stopped (if ongoing) and the Personal Consultee asked whether, in their opinion, the patient would be willing to continue with ongoing data collection.

Where a Personal Consultee is unable to visit the patient in hospital (e.g. due to infection control measures), this consultation may take place over the telephone. The consultation should be conducted by an experienced member of the site research team with knowledge of intensive care. The telephone consultation should be witnessed by another member of staff. The Personal Consultee Information Sheet may be sent to the Personal Consultee by email or by post. The outcome of the consultation will be documented and signed by person seeking opinion on the Personal Consultee Telephone Opinion Form, countersigned by the witness.

Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.4.2.1). The patient's decision will be final, and will supersede the Personal Consultee, where there is disagreement.

3.4.2.3 Nominated Consultee Opinion

In the situation where the patient has died, a Nominated Consultee will be appointed. The Nominated Consultee may include an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust or an independent doctor (i.e. not involved in the trial). Opinion of the Nominated Consultee will be sought in the same manner as for the Personal Consultee.

A Nominated Consultee will also be approached in the rare situations where no Personal Consultee is available (or one is available, but does not wish to be consulted). Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.4.2.1). The patient's decision will be final, and will supersede the Nominated Consultee, where there is disagreement.

3.4.2.4 Discharge prior to consent/opinion being confirmed

In the situation where the patient is discharged from hospital with mental capacity prior to confirming their consent decision, an experienced member of the site research team with knowledge of intensive care will attempt a phone call to the patient within 14 working days of

ultimate hospital discharge to: inform them of their involvement in UK-ROX; provide information about the trial; and seek their consent. The telephone consultation should be witnessed by another member of staff. The Patient Information Sheet may be sent to the patient by email or by post. The outcome of the telephone call will be documented and signed by person seeking consent on the Telephone Consent Form, countersigned by the witness.

If there is no response to at least three telephone call attempts, or, where no telephone number for the patient is documented, then the patient will be approached by post. The patient will be sent a covering letter, personalised by the most appropriate clinical/research team member, and a copy of the PIS and Postal Consent Form. The letter will direct the patient to the PIS for detailed information on the trial and provide contact details for if the patient wishes to discuss the trial further. In addition, the letter will confirm that if no Consent Form is received within four weeks of the letter being sent, then the participant's data will be included in the trial unless they notify the site research team otherwise.

Both methods described above will provide patients with the opportunity to opt-out of ongoing data collection or follow-up questionnaires. A decision to opt-out during the telephone call will be documented by the person seeking consent on the Telephone Consent Form. For the postal approach, the patient can actively opt-out by returning the Postal Consent Form or using the telephone contact details provided on the PIS, at any point during the trial.

If the participant is transferred to another hospital participating in UK-ROX before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

3.4.4 Refusal or withdrawals of consent/opinion

If a patient declines informed deferred consent, or a consultee advises that they believe the patient would not choose to participate in the trial, and, if a patient or their Consultee (Personal or Nominated) withdraws consent/opinion at any time during the trial - this decision will be respected and will be abided by. All data up to the point of this decision will be retained in the trial, unless the patient or consultee requests otherwise. Where possible, patients and consultees will be asked if they are happy for data to continue to be collected from the medical records for the trial, emphasizing that this will not require any further contact with the patient/consultee about the trial.

3.6 Interventions

See intervention clinical guidance figures in Appendix 2.

3.6.1 Intervention – conservative oxygen therapy [SpO₂ target of 90 (±2)%]

In the conservative oxygen therapy group, the lowest concentration of oxygen possible should be administered to maintain the patient's SpO₂ at 90 (±2)%.

Further guidance:

- For patients receiving oxygen, SpO₂ should not rise above 92%.
- Alarms should be set to prevent an SpO₂ lower than 88% and higher than 92%.

- SpO₂ should be compared to the SaO₂ measurements from arterial blood gas measurements (if being taken) and if there is a significant discrepancy between the two, the SaO₂ should be used in preference. A recent report has highlighted that in patients with pigmented skin, oxygen saturation probes can underestimate the degree of hypoxaemia (i.e. over-read).²⁴
- The intervention SpO₂ target should remain the same once a patient is extubated, regardless of the modality by which they receive oxygen therapy.
- If a participant is receiving 21% oxygen or breathing room air, maintaining an SpO₂ of 90 (±2)% may not be possible; in this instance 21% oxygen or room air should be continued, with the upper alarm limit deactivated.
- The intervention should be continued until discharge from ICU, or 90 days after randomisation, whichever is sooner.
- If a participant is readmitted to ICU within the 90 days, the intervention should be recommenced.
- If a patient requires high concentration oxygen to treat or prevent an acute life-threatening event (e.g. intubation, cardiopulmonary resuscitation) the intervention should be temporarily suspended during this time and the reason for the deviation recorded.
- If a patient develops a contraindication to conservative oxygen therapy (i.e. exclusion criteria - see section 3.2.2.) after randomisation, it will be at the discretion of the treating clinical team as to whether the conservative oxygen target is continued, with patient safety guiding this decision.

3.6.2 Control – usual oxygen therapy

Usual oxygen therapy is defined as local practice, as determined by the treating clinicians.

Further guidance:

- Clinicians should document the chosen SpO₂ target for the participant each day.
- A lower limit alarm can be set at the discretion of the treating clinician.
- An upper SpO₂ alarm must not be used.
- If a participant is readmitted to ICU within the 90 days, the intervention should be recommenced.

3.6.3 Co-interventions

All other usual care will be provided at the discretion of the treating clinical team. SpO₂ must be monitored continuously by pulse oximetry in both groups throughout the trial. Arterial blood gases can be taken from participants according to local practice but do not form part of this trial.

If a patient requires extracorporeal membrane oxygenation (ECMO) or hyperbaric oxygen treatment (HBOT) during the intervention period, the intervention will be terminated at that point.

3.7 Safety monitoring

3.7.1 Definitions

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).

Adverse Event

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

Serious Adverse Event

An adverse event is defined as serious if it:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.

“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.

“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.

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.

3.7.2 Assessment

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

3.7.2.1 Severity

- **None:** indicates no event or complication
- **Mild:** complications result in only temporary harm and do not require clinical treatment
- **Moderate:** complications require clinical treatment but do not result in prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitations to the patient
- **Severe:** complications require clinical treatment and results in prolongation of hospital stay and/or 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.

An event assessed as 'Severe' or 'Life-threatening' will be considered a Serious Adverse Event (SAE).

3.7.2.2 Relatedness

- **None:** there is no evidence of any relationship to the trial treatment
- **Unlikely:** there is little evidence to suggest a relationship to the trial treatment, and there is another reasonable explanation of the event
- **Possibly:** there is some evidence to suggest a relationship to the trial treatment, although the influence of other factors may have contributed to the event
- **Probably:** there is probable evidence to suggest a relationship to the trial treatment, and the influence of other factors is unlikely
- **Definitely:** there is clear evidence to suggest a relationship to the trial treatment, and other possible contributing factors can be ruled out.

3.7.2.3 Expectedness

- **Expected:** the event is listed as an expected SAE in Appendix 3
- **Unexpected:** the event is not listed as an expected SAE in Appendix 3.

3.7.3 Recording and reporting procedures

Occurrences of the specified, expected Serious Adverse Events (SAEs) will be recorded and reported for all randomised patients from the time of randomisation until ICU discharge or 90 days (whichever comes first). If a patient is readmitted to ICU within the 90 days, safety monitoring will be recommenced.

Considering that all eligible patients are critically ill and at increased risk of experiencing multiple adverse events due to the complexity and severity of their condition²⁵ – occurrences of non-

specified, unexpected, SAEs will only be reported if they are considered to have reasonably occurred as a consequence of oxygen therapy (i.e. not events that are part of the natural history of the primary disease process or expected complications of critical illness).

The following event(s) will not be reported as SAEs as they are collected as trial outcomes:

- Death (note that death itself should not be reported as an SAE, but the suspected cause of death should be assessed for severity, relatedness and expectedness as detailed above)

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported to ICNARC CTU. 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 and reported to the ICNARC CTU using the UK-ROX SAE Report Form, by email to uk-rox@icnarc.org, 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 UK-ROX 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 UK-ROX TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

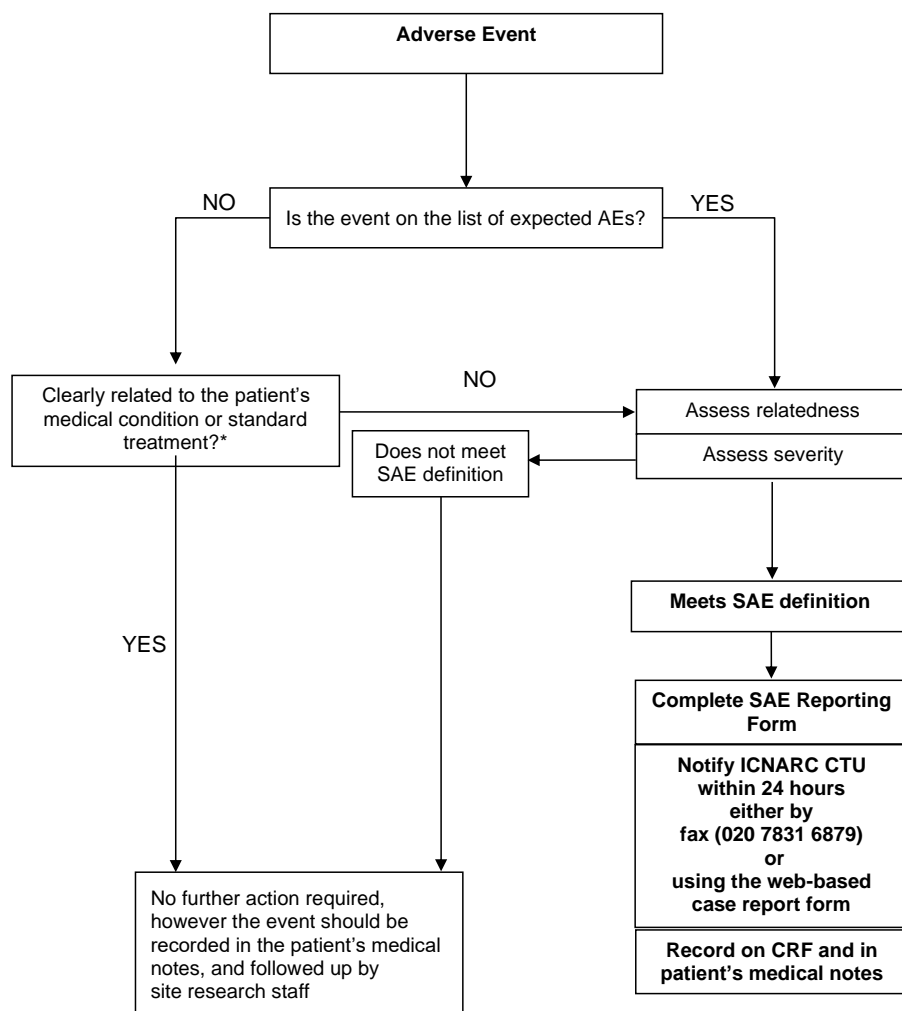
All other adverse events that occur between randomisation and 90 days post-randomisation (or ICU discharge, if sooner) must be recorded in the participant's medical notes.

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

3.7.4 Notifying the Research Ethics Committee

SAEs that do not require expedited reporting will be reported in the annual progress report submitted by the ICNARC CTU to the REC, commencing one year from the date of approval for the trial.

Figure 1: Adverse Event recording and reporting



*If there is any uncertainty about whether the SAE is associated with trial treatment, then it should be reported.

3.8 Data collection

For the vast majority of patients (n=14,000), only a minimal, basic level of primary data collection will be conducted, whilst an enhanced level of data collection will be on 2,500 (15%) patients (see *Table 1*). In total, 85% of all trial data fields will come from routine data sources.

3.8.1 CMP data – all patients

All trial data collection will be nested within the CMP 'Research Platform', enabling data collection to be incorporated within the routine CMP data collection processes, streamlining data linkage. For all patients, UK-ROX will nest within the routine data collection for the CMP, including:

- baseline demographics and risk factors;
- secondary outcomes of ICU and acute hospital mortality, duration of ICU and acute hospital stay; and
- critical care costs, based on Health Care Resource Groups, from the index admission and any subsequent critical care readmissions.

3.8.2 Other routine data sources – all patients

Data from other routine sources will be obtained for all consenting patients, including:

- date of death by data linkage with civil registrations mortality data held by NHS Digital; and
- hospital costs for subsequent hospitalisations, by data linkage to Hospital Episode Statistics held by NHS Digital and Patient Episodes Data for Wales held by the NHS Wales Informatics Service.

3.8.3 Basic primary data collection – all patients

A basic level of data collection will be carried out for all patients, with data items collected at each site specifically for the trial limited to:

- confirmation of eligibility criteria and patient consent/consultee opinion; and
- SAE reporting (if applicable).

3.8.4 Enhanced primary data collection

An enhanced level of data collection will be carried out for 2,500 (15%) patients, including prospectively for the first 10 patients at each site (to identify early issues and inform the internal pilot), followed by retrospective chart abstraction of SpO₂, FiO₂, PaO₂ and SaO₂ measurements from randomly sampled patients across sites, treatment groups and the course of the trial. HrQoL at 90 days will be measured on survivors from this same sample.

Table 1. Basic and enhanced primary data collection schedule.

	Level of data collection	
	Basic	Enhanced
Patients	14,000 / 16,500	2,500 / 16,500
<i>Collected in-hospital</i>		
Eligibility/randomisation data	✓	✓
Consent/opinion data	✓	✓
Patient contact details		✓
Intervention/adherence data		✓
Serious Adverse Event (SAE) data	✓	✓
<i>Collected at follow-up</i>		
HrQoL (EQ-5D-5L) at 90 days		✓
Health services/resource use at 90 days		✓
<i>Collected through data linkage</i>		
Mortality data	✓	✓
Health services/resource use	✓	✓

3.8.5 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 the sites. The site PIs 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 PIs to qualified members of the research team.

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.

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. ICNARC is registered under the Data Protection Act (Registration number: Z6289325).

3.9 Questionnaire follow-up

As part of the enhanced data collection - surviving, consenting patients will be followed up with a questionnaire at 90-days following randomisation.

Survival status at 90 days will be ascertained through participating sites and/or data linkage with nationally-held civil registrations deaths data. Survivors will be posted a questionnaire by the ICNARC CTU containing the EQ-5D-5L and health services questionnaire. The questionnaire is designed to take no longer than 15 minutes to complete and patients will be provided with a pen and self-addressed stamped envelope for ease of return. The covering letter sent with the questionnaire will provide patients with the option to complete the questionnaire online, if preferred. If patients wish to complete the questionnaire online they will be prompted to scan a QR code using their smartphone or tablet, which will link to the online questionnaire.

Non-responders will be telephoned three weeks after the questionnaire was posted and asked to check whether they have received the questionnaire. If preferable for the patient, they will be offered the option of either being sent another copy of the questionnaire in the post, completing the questionnaire over the telephone with a trained member of the UK-ROX team, or, to receive the questionnaire in a preferred alternative format (e.g. email).

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 patient and conduct the questionnaire with them in hospital, if willing and their condition permits. If a patient is on their initial acute hospital admission at the follow-up time point, they will not be asked to complete the health services questionnaire, as this contains only questions that are relevant following discharge from acute hospital.

3.9.1 'Thank you' card Study Within A Trial

A Study Within A Trial (SWAT) will be implemented as part of the questionnaire follow-up. The purpose of the SWAT is to evaluate the impact of sending a personalised 'Thank you' card alongside the regular trial follow-up, on questionnaire response rate. The card will be trial-branded and will be personalised, with the patient's name and a sign off from a member of the trial team, handwritten in wet ink. Patients will be randomised 1:1 to receive the 'Thank you' card (intervention) or not (control). All other aspects of questionnaire follow-up process will remain the same. Outcomes to be investigated in the SWAT include: proportion of patients completing the follow-up questionnaire, time to response and level of data completeness in returned questionnaires.

If a patient is an in-patient at a participating site at the follow-up time-point, they will not be included in the 'Thank you' card SWAT.

3.10 Outcomes

3.10.1. Internal pilot

An internal pilot will run from months 10-15 (as per the grant timeline), using a traffic light system to assess key progression criteria regarding sites opening, recruitment, separation and adherence to the protocol.²⁶

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.

Table 2. Internal pilot progression criteria.

	Green	Amber	Red
Number of sites open to recruitment	>50	20-50	<20
Recruitment rate (per site, per month)	≥75% of anticipated	40-75% of anticipated	<40% of anticipated
Separation in median measurements between groups	SpO ₂ : ≥3% OR FiO ₂ : ≥0.1	(SpO ₂ : 1.5-3% AND FiO ₂ : < 0.1) OR (SpO ₂ : < 3% AND FiO ₂ : 0.05 – 0.09)	SpO ₂ : <1.5% AND FiO ₂ : <0.05
Treatment adherence*	≥75% cases	50-75% cases	<50% cases

*Defined as adjustments to ventilator settings or supplemental oxygen as per protocol

3.10.2. Outcome measures

Primary outcome - clinical evaluation:

- 90-day all-cause mortality.

Primary outcome – economic evaluation:

- Incremental costs, QALYs and net monetary benefit at 90 days.

Clinical evaluation secondary outcomes:

- ICU and hospital mortality (censored at 90 days)
- Mortality at 60 days and one year
- Duration of ICU and acute hospital stay (censored at 90 days)
- HrQoL, assessed using the EuroQol EQ-5D-5L questionnaire,²⁷ at 90-days.

Economic evaluation secondary outcomes:

- HrQoL, assessed using the EuroQol EQ-5D-5L questionnaire,²⁷ at 90-days
- Resource use and costs at 90 days
- Estimated lifetime incremental cost-effectiveness.

4. Statistics and data analysis

4.1 Sample size

Based on data from potentially eligible patients in the CMP (N=96,028, April 2017 to March 2019) and the Risk II study dataset (N=82,075, April 2014 to March 2016), 90-day all-cause mortality is anticipated to be 37%. To detect an absolute and clinically important risk reduction of 2.5% (relative risk reduction 6.8% - a conservative treatment effect which is smaller than that

observed in our updated meta-analysis of critical care trials) in 90-day all-cause mortality from 37% to 34.5% with 90% power requires a total sample size of 15,444 patients. Allowing for 6% refusal of consent/withdrawal/loss to follow-up (based on figures from the 65 Trial²⁸), we will recruit a total of 16,500 patients.

Based on data from the CMP, a recruitment rate of 8 patients per unit per month (half of the observed median rate of potentially eligible patients) will allow recruitment of the full sample within two years from 100 ICUs, allowing for a staggered opening of sites over a 6-month period.

4.2 Statistical analysis

4.2.1. Internal pilot analysis

Data will be analysed at the end of the internal pilot trial stage (months 10-15 of the grant timeline). The analysis will take place in month 17 of the grant to allow data to be collected and entered to assess all progression criteria. If all the green criteria are met, the trial will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, the trial will be amended to address the issues raised. If any of the red criteria are met, the trial will stop.

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.

4.2.2 Clinical effectiveness analysis

All analyses will be lodged in a statistical analysis plan, *a priori*, before the investigators are unblinded to any trial 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 subject to statistical testing. The delivery of the intervention will be described in detail. Results will be reported in accordance with the CONSORT statement.²⁹

Analysis of the primary outcome (90-day all-cause mortality) will be performed both adjusted only for site, hypoxic ischaemic encephalopathy, acute brain pathologies (excluding hypoxic ischaemic encephalopathy) and sepsis (as stratification variables) and adjusted for additional baseline covariates. The primary analysis of the primary outcome will be adjusted for the stratification variables and other pre-specified risk factors. Effect estimates will be estimated using regression models incorporating site random effects, and the absolute risk reduction and relative risk reported. Adjustment for baseline covariates can increase the precision of the estimate of treatment effect, and therefore the power of the trial, and adjust for any chance imbalance between the treatment groups. The covariates for inclusion in the adjusted analysis will be selected *a priori* based on established relationship with outcome for critically ill patients, and not because of observed imbalance, significance in univariable analyses or by stepwise selection method.

Analyses of secondary outcomes will use similar regression models with the binomial/Poisson family for binary outcomes and normal family for continuous outcomes. Analyses of duration of critical care unit and acute hospital stay will be performed by Wilcoxon rank-sum tests, stratified by survival status. Survival will be presented as Kaplan-Meier plots and analysed by Cox proportional hazards models with shared frailty at the site level.

Subgroup analyses will test for an interaction between treatment group and subgroup (for a limited number of subgroups specified *a priori*) in the adjusted regression models for the primary

outcome. Key subgroups will include: Suspected hypoxic-ischaemic encephalopathy; acute brain injury (excluding hypoxic-ischaemic encephalopathy); and sepsis.

Two interim analyses will be carried out after the recruitment and 90-day follow-up of 4,500 and 10,000 patients using a Peto-Haybittle stopping rule ($P < 0.001$) to recommend early termination due to either effectiveness or harm. Further interim analyses will be performed if requested by the DMEC.

4.2.3 Health economic evaluation

A full cost-effectiveness analysis (CEA) will be undertaken to assess the relative cost-effectiveness of the use of the intervention (conservative oxygen therapy) versus control (usual oxygen therapy) according to intention to treat principle. Patient level resource use and outcome data collected as a part of the trial linked with CMP and hospital episode statistics (HES) databases will be used to report cost-effectiveness at 90 days.

The CEA will take a health and personal health services perspective and will measure resource use associated with delivering the intervention, length of stay in critical care and acute hospital, and use of personal health services. Information on resource use associated with interventions will be obtained from detailed in-patient data collection on 15% trial participants selected for intervention/adherence monitoring. These patients will be followed up with health services and EuroQol EQ-5D-5L questionnaires to assess their use of primary care and community health services and HrQoL. The CEA will develop regression model to predict resource use associated with the interventions, and the use of primary and community health services. The regression models will be validated and used to predict resource use for all patients in the trial. 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 calculate total costs per patient for up to 90 days since randomisation.

HrQoL at 90 days will be assessed from 15% of trial participants selected for follow-up questionnaire using the EuroQol EQ-5D-5L questionnaire, which will be valued using appropriate EQ-5D-5L value set. HrQoL for all patients will be predicted by following a similar approach outlined for the costs as above. HrQoL data will be combined with the survival data to report QALYs at 90 days. QALYs will be calculated by valuing each patient's survival time by their HrQoL at 90 days according to the "area under the curve" approach. For 90-day survivors, QALYs will be calculated using the EQ-5D scores at 90 days, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and 90 days. For decedents between randomisation and 90 days, we will assume zero QALYs.

Net monetary benefits will be calculated by valuing QALY gains at £20,000 per QALY and subtracting incremental costs.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 90 days since randomisation. 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 perform extensive sensitivity analysis to check the robustness of primary cost-effectiveness results at 90 days. The cost-effectiveness results at 90 days will be reported across all subgroups as included for the clinical outcome analysis.

Lifetime cost-effectiveness will be projected by summarising the relative effects of alternative strategies on long-term survival, and HrQoL as compared with that of age-gender matched general population. The survival of the patients who survive the initial acute hospital episode and all readmissions to the same critical care unit up 90 days post randomisation will be extrapolated over lifetime. The extrapolation will assess the duration and magnitude of excess mortality of ICU patients relative to those of the age- and gender-matched general population, and will predict survival and HrQoL of the trial population for the period of excess mortality. After the period of excess mortality, age- and gender-matched general population survival and HrQoL will be applied. The lifetime costs will be projected by applying morbidity costs estimated at 90 days over the period of excess mortality. Predicted survival and HrQoL will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care.

5. Monitoring and auditing

5.1 Central monitoring

The ICNARC CTU will communicate regularly with sites via email, telephone, teleconferences and newsletters. This will include central review of consent forms and essential documents. Data will be actively and regularly reviewed centrally and local PIs will be contacted regularly to ensure adherence and the quality of the data.

5.2 Site monitoring

The on-site monitoring plan will follow a risk-based strategy. The timing and frequency of subsequent visits will be based on a risk assessment, including an assessment of each site's performance and local research team (e.g. experience of conducting RCTs). 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. Following all site visits, a report will be sent to the site summarising the visit, documents reviewed and the findings. Information learned from the site visits will be used to refine the trial procedures, as required, to ensuring clarity and consistency across sites.

6. Trial closure

6.1 End of trial

The end of the trial is defined as last patient, last 90-day follow-up. At this point, the 'Declaration of end of trial' form will be submitted to the REC by the ICNARC CTU.

6.1.1 Early discontinuation of the trial

The number of interim analyses will be limited to detect early evidence of harm and irrefutable mortality differences. Two interim analyses will be carried out after the recruitment and follow-up of 4500 and 10,000 patients using a Peto-Haybittle stopping rule ($P < 0.001$) to recommend early termination due to either effectiveness or harm. Further interim analyses will be performed if requested by the DMEC.

6.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all necessary centrally held trial-related documents for 5 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 5 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 site complied with the principles of ICH-GCP and other applicable regulatory requirements. Guidance on archiving will be provided to sites in a trial-specific SOP.

All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

7. Trial management and oversight

The Lead Investigators (Professor Daniel Martin and Mr Paul Mouncey) will take overall responsibility for the delivery of UK-ROX and oversee progress against timelines/milestones.

7.1 Good research practice

UK-ROX will be managed by the ICNARC CTU according to the Medical Research Council's Good Research Practice: Principles and Guidelines,³⁰ based on the principles of the International Conference on Harmonization guidelines on Good Clinical Practice³¹ and the UK Policy Framework for Health and Social Care Research.³² ICNARC policies and procedures are based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

7.2 Trial Management Group (TMG)

The TMG comprises the UK-ROX Investigators (see *UK-ROX Investigators*, page 5) and will be led by Lead Investigators (Professor Daniel Martin and Mr Paul Mouncey). Meeting of the TMG will be held quarterly, or more frequently during key stages of the trial, to ensure effective communication.

The day-to-day trial team will be led by the Trial Manager (Mr Alvin Richards-Belle) and comprise the Lead Investigators (Professor Daniel Martin and Mr Paul Mouncey), Clinical Trials Unit co-investigators (Professor Kathy Rowan, Professor David Harrison, Dr Doug Gould, Dr James Doidge), alongside the Trial Statistician, Research Assistant and Data Manager. The day-to-day trial team will meet regularly to discuss and monitor progress.

7.3 Trial Steering Committee (TSC)

A TSC will be established in line with the latest NIHR HTA guidelines (i.e. consist of 75% independent members – including the Chair). The Trial Steering Committee will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that it is conducted in accordance with the relevant guidelines and regulations. The Trial Steering Committee will comprise the Lead Clinical Investigator (Professor Daniel Martin) plus independent members (including a patient and public involvement (PPI) representative(s)). The first TSC meeting will be held prior to the start of patient recruitment, the second following completion of the internal pilot and then at any other time determined by the independent Chair, but at least annually.

7.4 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be set-up to monitor recruitment and retention, intervention adherence, separation and patient safety. Meetings will take place immediately prior to TSC meetings.

8. Ethics, approvals and dissemination

8.1 Ethical compliance

UK-ROX will be conducted in accordance with the: terms of the favourable ethical opinion; the approved trial protocol; ICH-GCP guidelines; the UK Data Protection Act; the Mental Capacity Act; and ICNARC CTU research policies and procedures.

UK-ROX has received a favourable ethical opinion from the South Central – Oxford C Research Ethics Committee (Reference: 20/SC/0423) and approval from the Health Research Authority ((Integrated Research Application System (IRAS) number: 260536).

8.1.1 Local ethical compliance

It is the responsibility of the site PI to obtain the necessary local approvals to run UK-ROX at their site, including confirmation of capacity and capability. Evidence of confirmation of capacity and capability must be provided to the ICNARC CTU prior to site activation (*see section 3.2.4*).

8.2 Trial registration

This trial has been registered with the ISRCTN Registry (ISRCTN13384956).

8.4 Patient and Public Involvement (PPI)

One co-investigator is a PPI representative who has actively contributed to the trial design and procedures, including the use of deferred consent. In addition, independent PPI representative(s) will be sought for membership of the TSC.

8.5 Data protection and participant confidentiality

Identifiable patient data, including full name, contact details, date of birth and NHS number will be required by the ICNARC CTU to successfully enable data linkage and follow-up participants. The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. We will seek consent to share the patients' anonymised data. All data will be stored securely. ICNARC is registered under the Data Protection Act.

8.6 Declaration of interests

All trial investigators have confirmed that they have no financial or other conflicts of interest to declare in relation to this trial.

8.7 Dissemination

The results of UK-ROX will be widely and actively disseminated. Results will be presented at: regional critical care network meetings; national professional conferences; the ICNARC Case Mix Programme Annual Conference; the Annual Meeting of the UK Critical Care Research Forum; and national and international critical care conferences/meetings.

A Trial Report to the NIHR HTA Programme will present a detailed description of the trial and its results, along with recommendations for future policy, practice and research. Articles will be prepared for publication in peer-reviewed scientific journals and in relevant professional journals.

8.7.1 Access to the final trial dataset

Once the data from the trial are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.

9. Sponsorship and funding

9.1 Sponsorship and indemnity

ICNARC is Sponsor for UK-ROX and holds professional indemnity insurance (Marsh Insurance Brokers Limited) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

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

9.2 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: NIHR130508).

10. Exploring pulse oximeter Accuracy across sKin Tones (EXAKT) sub-study

The EXAKT sub-study (NIHR152078) is a Study Within A Trial (SWAT) that aims to determine the effect of skin tone on the diagnostic accuracy of pulse oximeters in adult patients. Only selected UK-ROX sites are participating in the EXAKT sub-study. Please refer to the separate EXAKT study protocol addendum for detailed information.

119. References

1. 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. *Critical care (London, England)* 2008;**12**:R156. <https://doi.org/10.1186/cc7150>
2. Martin D, Grocott M. Oxygen therapy and the Goldilocks principle. *J Intensive Care Soc* 2017;**18**:279-81. <https://doi.org/10.1177/1751143717712162>
3. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, *et al.* Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet (London, England)* 2018;**391**:1693-705. [https://doi.org/10.1016/s0140-6736\(18\)30479-3](https://doi.org/10.1016/s0140-6736(18)30479-3)
4. Siemieniuk RAC, Chu DK, Kim LH-Y, Güell-Rous M-R, Alhazzani W, Soccia PM, *et al.* Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018;**363**:k4169. <https://doi.org/10.1136/bmj.k4169>
5. 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**:1583-9. <https://doi.org/10.1001/jama.2016.11993>
6. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, *et al.* Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med* 2020;**382**:989-98. <https://doi.org/10.1056/NEJMoa1903297>
7. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, *et al.* Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2020;**382**:999-1008. <https://doi.org/10.1056/NEJMoa1916431>
8. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Critical care medicine* 2013;**41**:423-32. <https://doi.org/10.1097/CCM.0b013e31826a44f6>
9. Helmerhorst HJ, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, *et al.* Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care. *Critical care medicine* 2017;**45**:187-95. <https://doi.org/10.1097/ccm.0000000000002084>
10. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, *et al.* Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive care medicine* 2012;**38**:91-8. <https://doi.org/10.1007/s00134-011-2419-6>
11. Palmer E, Post B, Klapaukh R, Marra G, MacCallum NS, Brealey D, *et al.* The Association between Supraphysiologic Arterial Oxygen Levels and Mortality in Critically Ill Patients. A Multicenter Observational Cohort Study. *Am J Respir Crit Care Med* 2019;**200**:1373-80. <https://doi.org/10.1164/rccm.201904-0849OC>
12. Aggarwal NR, Brower RG, Hager DN, Thompson BT, Netzer G, Shanholtz C, *et al.* Oxygen Exposure Resulting in Arterial Oxygen Tensions Above the Protocol Goal Was Associated With Worse Clinical Outcomes in Acute Respiratory Distress Syndrome. *Critical care medicine* 2018;**46**:517-24. <https://doi.org/10.1097/ccm.0000000000002886>
13. Ni YN, Wang YM, Liang BM, Liang ZA. The effect of hyperoxia on mortality in critically ill patients: a systematic review and meta analysis. *BMC pulmonary medicine* 2019;**19**:53. <https://doi.org/10.1186/s12890-019-0810-1>

14. Martin D, Grocott M, Bellomo R. Oxygenation targets in acutely ill patients: still a matter of debate. *Lancet (London, England)* 2018;**392**:2436. [https://doi.org/10.1016/s0140-6736\(18\)32219-0](https://doi.org/10.1016/s0140-6736(18)32219-0)
15. Asfar P, Schortgen F, Boissrame-Helms J, Charpentier J, Guerot E, Megarbane B, *et al.* Hyperoxia and hypertonic saline in patients with septic shock (HYPER2S): a two-by-two factorial, multicentre, randomised, clinical trial. *The Lancet Respiratory medicine* 2017;**5**:180-90. [https://doi.org/10.1016/s2213-2600\(17\)30046-2](https://doi.org/10.1016/s2213-2600(17)30046-2)
16. 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**:43-51. <https://doi.org/10.1164/rccm.201505-1019OC>
17. ICNARC. *Case Mix Programme Summary Statistics*.; 2019. URL: <https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports/Summary-Statistics> (accessed 17 August, 2020).
18. Intensive Care National Audit and Research Centre. *ICNARC report on COVID-19 in critical care*. London, UK: ICNARC; 2020.
19. Richards-Belle A, Orzechowska I, Gould DW, Thomas K, Doidge JC, Mouncey PR, *et al.* COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. *Intensive care medicine* 2020;**46**:2035-47. <https://doi.org/10.1007/s00134-020-06267-0>
20. Martin DS, Brew-Graves C, McCartan N, Jell G, Potyka I, Stevens J, *et al.* Protocol for a feasibility randomised controlled trial of targeted oxygen therapy in mechanically ventilated critically ill patients. *BMJ Open* 2019;**9**:e021674-e. <https://doi.org/10.1136/bmjopen-2018-021674>
21. Martin DS, McNeil M, Brew-Graves C, Filipe H, O'Driscoll R, Stevens JL, *et al.* A feasibility randomised controlled trial of targeted oxygen therapy in mechanically ventilated critically ill patients. *Journal of the Intensive Care Society* 2021; 10.1177/17511437211010031:17511437211010031. <https://doi.org/10.1177/17511437211010031>
22. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krlaza-Jeric K, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;**158**:200-7. <https://doi.org/10.7326/0003-4819-158-3-201302050-00583>
23. Authority HR. Joint Statement on the Application of Good Clinical Practice to Training for Researchers. 2017.
24. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial Bias in Pulse Oximetry Measurement. *New England Journal of Medicine* 2020;**383**:2477-8. <https://doi.org/10.1056/NEJMc2029240>
25. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2008;**178**:1181-4. <https://doi.org/10.1503/cmaj.071366>
26. Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, *et al.* Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;**7**:e013537. <https://doi.org/10.1136/bmjopen-2016-013537>

27. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727-36. <https://doi.org/10.1007/s11136-011-9903-x>
28. Lamontagne F, Richards-Belle A, Thomas K, Harrison DA, Sadique MZ, Grieve RD, *et al.* Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. *Jama* 2020;**323**:938-49. <https://doi.org/10.1001/jama.2020.0930>
29. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332. <https://doi.org/10.1136/bmj.c332>
30. Medical Research Council. *Good research practice: Principles and guidelines*. 2012. URL: <https://www.mrc.ac.uk/publications/browse/good-research-practice-principles-and-guidelines/> (accessed 2018).
31. INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE. GUIDELINE FOR GOOD CLINICAL PRACTICE. 1996
32. Health Research Authority. UK policy framework for health and social care research. 2017.

Appendix 1 – Protocol version history.

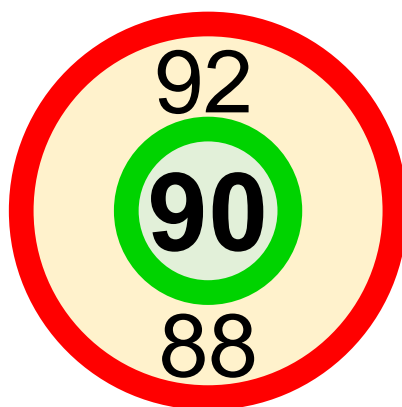
Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.1	14 December 2020	-	Initial approved version
SA001	1.2	19 March 2021	Daniel Martin Alvin Richards-Belle	<ul style="list-style-type: none"> Section 3.6.1: Previously, the intervention was described as "conservative oxygen therapy [SpO2 target range of 90-93%]." Now, the intervention is described as "conservative oxygen therapy [SpO2 target of 90 (± 2)%]". Guidance on delivery of the intervention has therefore been updated accordingly. Section 3.10.1: The start of the internal pilot has been changed from month 7 to month 10 (of the grant timeline), following approval from the funder (NIHR HTA Programme). Section 6.1: The definition of the end of the trial was corrected from "last patient, last follow-up" to "last patient, last 90-day follow-up." Other minor administrative changes and corrections.
SA002	1.3	15 July 2021	Alvin Richards-Belle	<ul style="list-style-type: none"> Addition of Section 3.9.1: 'Thank you' card Study Within A Trial. Other minor administrative changes and corrections.
SA003	1.4	17 February 2022	Lorna Miller	<ul style="list-style-type: none"> Section 3.9: Updated to indicate that patients will be provided with the option to complete the questionnaire follow-up online via a QR code.
<u>SA004</u>	<u>1.5</u>	<u>12 April 2022</u>	<u>Tasnin Shahid</u>	<ul style="list-style-type: none"> <u>Addition of section 10: 'Exploring pulse oximeter Accuracy across sKin Tones (EXAKT) sub-study'. The section briefly outlines the sub-study and references the protocol addendum for further information.</u> <u>Separate EXAKT study protocol addendum created for detailed information about the sub-study.</u>

Formatted: Space After: 0 pt

Appendix 2. Clinical guidance for trial interventions.



**CONSERVATIVE OXYGEN
THERAPY**
When receiving oxygen



Set upper alarm to prevent
an SpO₂ >92%

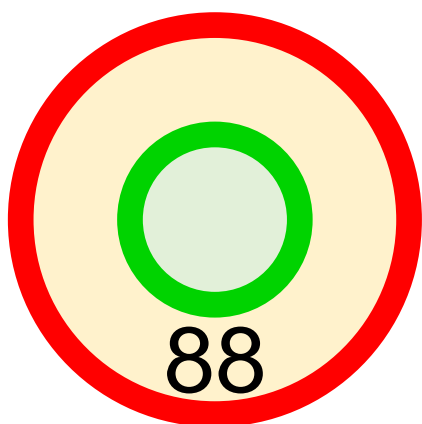
Reduce FiO₂ until SpO₂ is 90%

Set lower alarm to prevent
an SpO₂ <88%



CONSERVATIVE OXYGEN THERAPY

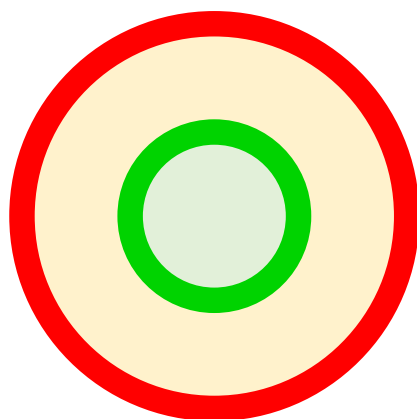
When on 21% oxygen or breathing room air



Set lower alarm to prevent
an SpO₂ <88%



USUAL CARE



An upper SpO₂ alarm should not be set

Oxygenation target should be set by the clinical team

lower alarm limit should be set by the clinical team

Appendix 3 - Expected adverse events.

Expected SAEs that could be observed in participants up to critical care discharge following randomisation:

- sinus tachycardia
- supraventricular tachycardia
- atrial fibrillation
- myocardial ischaemia/infarction
- mesenteric ischaemia

If an SAE, as defined in Section 3.7, occurs this should be recorded and reported as described in Section 3.7.