

## Welcome to the Integrated Research Application System

## IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

**Please enter a short title for this project** (maximum 70 characters)

UK-ROX

**1. Is your project research?**

Yes  No

**2. Select one category from the list below:**

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

**If your work does not fit any of these categories, select the option below:**

Other study

**2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?**

Yes  No

**2b. Please answer the following question(s):**

- a) Does the study involve the use of any ionising radiation?  Yes  No
- b) Will you be taking new human tissue samples (or other human biological samples)?  Yes  No
- c) Will you be using existing human tissue samples (or other human biological samples)?  Yes  No

**3. In which countries of the UK will the research sites be located?** *(Tick all that apply)*

- England  
 Scotland  
 Wales  
 Northern Ireland

**3a. In which country of the UK will the lead NHS R&D office be located:**

- England  
 Scotland  
 Wales  
 Northern Ireland  
 This study does not involve the NHS

**4. Which applications do you require?**

- IRAS Form  
 Confidentiality Advisory Group (CAG)  
 Her Majesty's Prison and Probation Service (HMPPS)

**5. Will any research sites in this study be NHS organisations?**

- Yes  No

**5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?**

Please see information button for further details.

- Yes  No

*Please see information button for further details.*

**5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?**

Please see information button for further details.

- Yes  No

*The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".*

*If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.*

**6. Do you plan to include any participants who are children?**

Yes  No

**7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?**

 Yes  No

*Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.*

**8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?**

 Yes  No

**9. Is the study or any part of it being undertaken as an educational project?**

 Yes  No

**10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?**

 Yes  No

**11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?**

 Yes  No

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**Integrated Research Application System**  
**Application Form for Other clinical trial or investigation**


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**IRAS Form (project information)**

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)  
UK-ROX

Please complete these details after you have booked the REC application for review.

**REC Name:**  
South Central - Oxford C Research Ethics Committee

**REC Reference Number:**  
20/SC/0423

**Submission date:**  
29/10/2020

**PART A: Core study information**
**1. ADMINISTRATIVE DETAILS**
**A1. Full title of the research:**

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

**A3-1. Chief Investigator:**

	Title	Forename/Initials	Surname
	Professor	Daniel	Martin
Post	Professor of Perioperative and Intensive Care Medicine		
Qualifications	BSc, MBChB, FRCA, FFICM, PhD		
ORCID ID	0000 0001 6220 8235		
Employer	University of Plymouth		
Work Address	John Bull Building		
	Derriford		
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Post Code	PL6 8BU		
Work E-mail	daniel.martin@plymouth.ac.uk		
* Personal E-mail			
Work Telephone	02072699277		

\* Personal Telephone/Mobile  
Fax

*\* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.  
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.*

**A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?**  
*This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.*

	Title Forename/Initials Surname
	Mr Alvin Richards-Belle
Address	ICNARC CTU Napier House, 24 High Holborn London
Post Code	WC1V 6AZ
E-mail	uk-rox@icnarc.org
Telephone	02072699277
Fax	

**A5-1. Research reference numbers.** *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):  
 Sponsor's/protocol number: 01/10/20  
 Protocol Version: 1.0  
 Protocol Date: 26/10/2020  
 Funder's reference number (enter the reference number or state not applicable): NIHR130508  
 Project website: <https://www.icnarc.org/Our-Research/Studies/Uk-Rox>

**Registry reference number(s):**

*The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.*

International Standard Randomised Controlled Trial Number (ISRCTN):  
 ClinicalTrials.gov Identifier (NCT number):

**Additional reference number(s):**

Ref.Number	Description	Reference Number
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**A5-2. Is this application linked to a previous study or another current application?**

Yes  No

*Please give brief details and reference numbers.*

The Targeted OXYgen therapY in Critical illness (TOXYC) (REC Reference: 17/LO/1334)

**2. OVERVIEW OF THE RESEARCH**

*To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.*

**A6-1. Summary of the study.** *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Each year, around 184,000 patients are admitted to NHS intensive care units (ICUs) and over 30% require help with their breathing using a ventilator (breathing machine). Giving oxygen through the ventilator is an essential part of this treatment. However, we do not know how much oxygen should be given to patients to optimise their recovery. Both too much, and too little, oxygen may cause harm. The concentration of oxygen given through the ventilator is adjusted according to how much oxygen can be detected in a patient's blood, known as 'oxygen saturation'. Some studies have shown that in unwell hospitalised patients, having a lower, rather than higher, oxygen saturation may more be beneficial.

We therefore intend to conduct a large clinical trial to find out whether using a lower oxygen target (conservative oxygen therapy) to guide oxygen treatment might lead to better outcomes for patients when compared with the approach currently used in NHS ICUs (usual oxygen therapy). The study will include 16,500 patients from 100 UK NHS ICUs. Patients will be randomly assigned to either the conservative oxygen therapy or usual oxygen therapy group. We will follow all patients up to 90 days later by 'linking' study data with routinely collected national records. We will find out if conservative oxygen therapy was more effective than usual oxygen therapy by comparing the number of patients alive in each group at 90 days.

Patient recruitment will start early in 2021 and end in 2023. Results will have a large and immediate impact on ICU clinical practice and on patient outcomes throughout the NHS. Data from the 16,500 patients in this study will also contribute to a larger global study of 40,000 patients. The global study will answer similar questions about oxygen therapy in ICU patients but from an international perspective.

**A6-2. Summary of main issues.** *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

*Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.*

#### Purpose and design

Each year, around 184,000 patients are admitted to NHS intensive care units (ICUs). Over 30% of these patients will require help with their breathing using an invasive mechanical ventilator and supplemental oxygen. Giving oxygen through the ventilator is an essential part of this treatment, however, we do not know how much oxygen should be given to patients to help optimise their recovery. Both too much and, too little, oxygen may cause harm. The concentration of oxygen given to patients is adjusted according to how much oxygen can be detected in a patient's blood, known as 'oxygen saturation'. Some studies have shown that in unwell hospitalised patients, using a lower, rather than higher, oxygen saturation target to guide treatment may be more beneficial.

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. 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]?

The UK-ROX trial was designed by experts in critical care – both from clinical and methodological backgrounds. The Joint-Chief Investigators are Professor Daniel Martin OBE (Professor of Perioperative and Intensive Care Medicine at the University of Plymouth) and Mr Paul Mouncey (Head of Research at the Intensive Care National Audit & Research Centre (ICNARC)). The trial will be managed by the ICNARC Clinical Trials Unit (CTU), which has extensive experience in coordinating large and complex clinical trials in critical and emergency care settings. The Trial Management Group also includes a Patient and Public Involvement (PPI) representative (former ICU patient) who has and will provide vital patient engagement and has reviewed all patient materials used in the trial. The full Trial Management Group will meet regularly to review progress of the trial against timelines and milestones. In addition, the research proposal was reviewed by anonymous peer reviewers and recommended for funding by the National Institute for Health Research.

We recently 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 this patient population. UK-ROX also builds on the "ICU-ROX" trial which involved 1,000 patients in Australia and New Zealand. Learnings from these former studies has informed the design of UK-ROX.

#### Inclusion / Exclusion

The eligibility criteria for UK-ROX are designed to be as inclusive as possible: adults admitted to participating ICUs receiving invasive mechanical ventilation and supplemental oxygen. Eligible patients must be enrolled within 12 hours of fulfilling the eligibility criteria (listed below), reflecting the early nature of the intervention.

#### Inclusion criteria:

- Aged  $\geq 18$  years
- 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)
- Receiving supplemental oxygen (fractional inspired concentration of oxygen (FIO<sub>2</sub>)  $>0.21$ ) at the time of enrolment

#### Exclusion criteria:

- Previously randomised into UK-ROX in the last 90 days
- The clinician considers that one study treatment arm is either indicated or contraindicated. [A data dictionary will be provided to participating sites which contains relevant examples of conditions where clinicians may exclude patients (at their discretion) because conservative oxygen therapy is either indicated or contraindicated (e.g. chronic lung diseases, receiving hyperbaric oxygen, prior bleomycin exposure, carbon monoxide poisoning).]

#### Recruitment and consent

Patients will be screened for eligibility by local research and clinical teams (members of the direct health care team) at ICUs in NHS hospitals.

One of the main ethical issues in this trial is consent. The decision to start a patient on mechanical ventilation with supplemental oxygen in ICUs is made in a time-sensitive and life-threatening situation for the patient. This decision is not impacted by the trial i.e. patients only become eligible for the trial once their doctor has already started mechanical ventilation and oxygen therapy. Patients will lack mental capacity to provide informed consent at the point they become eligible for the trial by virtue of receiving invasive mechanical ventilation. Timely enrolment of eligible patients into the trial is paramount to ensure its scientific validity, specifically in terms of achieving the conservative oxygen targets in the intervention group. As such, early enrolment in the course of treatment will allow for generalisable conclusions to be drawn from the trial for the benefit of future ICU patients.

The moment in time when patients become eligible for the trial is likely to be very distressing for relatives. Relatives are likely to be distressed by the patient's illness and admission to ICU. It is therefore likely that relatives themselves may not have sufficient capacity to make an informed decision [of the patient's wishes about trial participation], in the short time frame available. The minimisation of additional potential stress to relatives has been a priority of the Trial Management Group in developing the proposed consent model.

The reasons outlined above make any attempt to obtain prior informed consent from patients or advice from a relative/close friend (Personal Consultee) inappropriate. Therefore, the trial team have discussed and worked through the consenting procedures with the investigators, in particular the Patient and Public Involvement (PPI) and research nurse co-investigators, at length to ensure acceptability, and propose a deferred consent (also known as 'research without prior consent') model for use in UK-ROX. [The consent procedure has also been designed to ensure feasibility in light of contemporary government and NHS restrictions due to the COVID-19 pandemic (e.g. reduced patient visiting by relatives)].

In brief, once a patient is screened as eligible for the trial (i.e. satisfies inclusion and exclusion criteria), they will be enrolled and randomised to receive the assigned treatment immediately. Patients in ICUs are monitored very closely and clinical/research staff working in this setting have extensive experience of assessing capacity in their patients. Once a patient has regained capacity, they will be approached by an authorised member of the site research team for informed deferred consent. This will be done as soon as practically possible (usually within 24 - 48 hours of the patient regaining capacity). In the interim period - once the patient's medical situation is deemed to no longer be an emergency, a Personal Consultee will be approached (in person or by telephone) to provide their opinion of the patient's wishes regarding participating in the trial.

Unfortunately, due to the nature of critical illness, some participants will pass away during their hospital admission. In the situation where the patient has died, or in the rare situation where no Personal Consultee is available (or one is available, but does not wish to be consulted) - a Nominated Consultee will be appointed. A Nominated Consultee could be an Independent Mental Capacity Advocate or an Independent Doctor who is not associated with the conduct

of UK-ROX. Agreement will be sought from the Nominated Consultee in the same manner as for the Personal Consultee. The decision to appoint a Nominated Consultee when a patient has passed away was made, following discussions and agreement with the PPI co-investigator, in light of burden on already grieving, upset and distressed relatives or close friends, and the potential to add further stress to them. However, authorised staff members at participating sites will be encouraged to discuss the trial with relatives or close friends of patients that have passed away, but will not prioritise the signing of an Opinion Form during this sensitive time.

Telephone and postal mechanisms for consent is also in place for the situation where patients are discharged from hospital prior to confirming their consent decision. The consent model proposed is similar to that of the recently completed 65 Trial (IRAS number: 215503). Further details on the consent procedures are provided in sections A29 and A30-1, Part B.6 (Adults unable to consent) and the Protocol.

#### Risks, burdens and benefits

We know that extremely high and extremely low oxygen levels can cause damage to our bodies. The purpose of this study is to look at the effect of a small reduction in how much oxygen we give. The benefits and risks of using both the slightly lower oxygen target compared to usual oxygen therapy are unclear at this time, and this is why this research is needed.

Patients in the usual oxygen therapy group will receive the same treatment, at the discretion of the local clinical team, that they would have received if they were not taking part in the trial and as such, it could be argued that there are no additional risks for this group.

Patients in both groups (conservative and usual oxygen therapy) will be closely monitored for serious adverse events that may be related to the trial treatments. Data on serious adverse events will be collected on all study participants. Safety will be monitored by the independent Data Monitoring and Ethics Committee (at a schedule deemed appropriate by the Committee) who will recommend the continuation (or not) of the trial to the majority-independent Trial Steering Committee.

As the trial will use identifiable and health data, there is a small risk that data could be lost or breached. Robust measure will be in place to prevent this from occurring – e.g. through the implementation of regular data back up arrangements and data disaster recovery procedures. To minimise the possibility of data security breaches, all data leaving the recruiting NHS hospital will be encrypted. Identifiable data will only be collected where essential. Participants will be allocated a unique Trial Number to minimise processing of identifiable data. Data sharing agreements will be put in place where needed (e.g. between ICNARC and NHS Digital to permit data linkage).

Potential risks and benefits of taking part in the trial will be fully detailed in the Patient Information Sheet and Consultee Information Sheets. Information from UK-ROX will ultimately help efforts to improve the treatment and outcomes of ICU patients.

One potential perceived burden to patients taking part in the trial could be the completion of follow-up questionnaires at 90 days. The questionnaire is designed to minimise burden and should take no longer than 15 minutes to complete at each time point. A self-addressed stamped envelope and pen will be included with questionnaire packs sent to patients for ease of return (and so there is no cost to patients). Information on the follow-up questionnaires will be provided on Patient Information Sheet and Consultee Information Sheets and patients will be presented with this as an option to consent (or not) for. We have also reduced the burden of this aspect of the trial by only aiming to send follow-up questionnaires to 15% of randomised patients. Therefore, the vast majority will not receive this questionnaire. For those receiving the questionnaire, ultimately, it will be their decision at that time as to whether they wish to complete the questionnaire or not. Our previous studies have achieved response rates ranging 75-80% of critical care survivors, suggesting this aspect is not unduly burdensome.

#### Confidentiality

Patient identifiable data (name and contact details) will be required at ICNARC CTU to enable the UK-ROX trial team to contact and follow-up patients at 90 days. These data will also be required to conduct 'data linkage' to NHS Digital and other national NHS data sources. Within a year of completion of the trial, all identifiable data will be anonymised. Only individuals vital to specific UK-ROX trial activities will have access to any identifiable data. ICNARC will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified to a third party. Data will be stored in a secure manner and all of ICNARC CTU trials and studies are carried out in accordance with the Data Protection Act 2018. Any data leaving the NHS will be encrypted.

#### Conflicts of interest

None

Use of tissue samples in future research

None

### 3. PURPOSE AND DESIGN OF THE RESEARCH

**A7. Select the appropriate methodology description for this research. Please tick all that apply:**

- Case series/ case note review
- Case control
- Cohort observation
- Controlled trial without randomisation
- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study
- Laboratory study
- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

**A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.**

The main objective is to evaluate the clinical effectiveness of conservative versus usual oxygen therapy on 90-day all-cause mortality (primary clinical effectiveness outcome).

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

**A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.**

Secondary objectives are to evaluate the clinical and cost-effectiveness of conservative versus usual oxygen therapy on:

- Incremental costs, QALYs and net monetary benefit at 90 days (primary cost-effectiveness 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

**A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.**

Patients admitted to an intensive care unit (ICU) who require assistance with their breathing from a mechanical ventilator (breathing machine) will receive oxygen as part of their treatment. This makes oxygen the commonest drug given to patients being treated on an ICU. Oxygen is vital to maintain life and when deprived of oxygen humans come to harm. However, oxygen can also cause harm if administered in excess. It is therefore important to optimise the amount of oxygen given to patients in order to minimise any potential harm. Despite its daily use on ICUs, we do not know how much is the right amount of oxygen to give to patients on a mechanical ventilator. Studies have shown that for some groups of unwell patients in hospital, giving slightly less oxygen than usual may achieve more favourable outcomes for patients. We do not know if this is true for those on a mechanical ventilator. A number of studies have been conducted to answer this question but to date, no clear answer has been forthcoming. If we are to be able to give

the right amount of oxygen to patients on a ventilator, then research must be conducted to provide the evidence on which guidance can be based. Therefore, we propose a large-scale, multi-centre study to address this knowledge gap by evaluating the clinical and cost-effectiveness of using a slightly lower oxygen target ('conservative oxygen therapy') than usual to patients on a ventilator. We will determine whether conservative oxygen therapy improves survival in mechanically ventilated patients admitted to ICUs in the UK. We have previously conducted a small feasibility study to determine whether such a study would be possible in the UK and have designed the current trial on what we learnt from that.

**A13. Please summarise your design and methodology.** *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

UK-ROX null hypothesis

Clinical evaluation: There is no effect of conservative oxygen therapy when compared to usual oxygen therapy on mortality at 90 days.

Economic evaluation: There is no effect of conservative oxygen therapy when compared to usual oxygen therapy on incremental costs, quality-adjusted life year and net monetary benefit (measures of cost-effectiveness) at 90 days.

Design and methodology

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. The trial plans to include 16,500 critically ill patients recruited from 100 NHS adult intensive care units (ICUs). The RCT design is considered the gold standard design for clinical trials.

Patients will be randomly allocated ("randomised"), in a 1:1 ratio, to one of two treatment groups: conservative oxygen therapy (intervention) or usual oxygen therapy (control). Each participant will have 50/50 chance of being enrolled in the intervention or control group.

It is necessary to include the usual oxygen therapy (control) group in the trial as patients in the conservative oxygen therapy group will be compared directly with those in the usual oxygen therapy group to see if the intervention is beneficial (or not) when compared with current NHS practice. This will ensure that the results can be directly applied to the NHS setting.

Patients receiving supplemental oxygen during invasive mechanical ventilation in ICUs will be eligible for the trial. The trial interventions are intended to be delivered early in the course of mechanical ventilation, just as would be the case in standard NHS practice, and therefore patients must be randomised within 12 hours of meeting the eligibility criteria. Patients identified after 12 hours will no longer be eligible for the trial. Prompt screening and randomisation of eligible patients will be crucial to the success of the trial.

If a patient is randomised to the usual oxygen therapy (control) group, the clinical team will continue to deliver oxygen therapy as per local practice and clinical management will not be influenced by the trial. 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 is randomised to conservative oxygen therapy (intervention) group, the clinical team will use an SpO<sub>2</sub> target range of 90-93%. the lowest concentration of oxygen possible should be administered to maintain the patient's SpO<sub>2</sub> at or just above 90%. For patients receiving oxygen, SpO<sub>2</sub> should not rise above 93%. Alarms should be set to sound at an SpO<sub>2</sub> of 89% and below and 94% and above. The intervention remains the same once a patient is extubated, regardless of the modality by which they receive oxygen therapy. 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.

In both groups, all other treatments and procedures will be carried out in accordance to standard NHS care and local practice.

As eligible patients will be critically ill and on an invasive mechanical ventilator at the point in which they become eligible for UK-ROX – a model of research without prior consent (RWPC) (also known as 'deferred consent') is proposed. This model has been chosen because invasive mechanical ventilation is a life-saving measure initiated during an emergency clinical situation, during which the vast majority of patients will lack the mental capacity to provide prospective informed consent. In brief, eligible patients will therefore be enrolled into the trial and followed up for consent when appropriate. This type of consent model is used in clinical trials comparing treatments in emergency

clinical situations (such as this one) to find out which is best. The specific model proposed for UK-ROX has been informed/approved by our Patient and Public Involvement (PPI) co-investigator. Full information about the deferred consent procedures are provided in detail in sections A6-2, A29 – A31 and Part B Section 6 (adults unable to consent) of the IRAS form.

At 90 days, 15% of participants will be posted a questionnaire about health-related quality of life and their use of health services since leaving hospital. These questionnaires have been used in previous ICU trials and will provide valuable information for the integrated economic evaluation. The questionnaire is designed to take no longer than 15 minutes to complete. A stamped addressed envelope and a pen will be included, so it will not cost the patient anything. A trained member of the UK-ROX team at the ICNARC CTU will telephone participants who have not returned the questionnaire after three weeks, to check if they have received it and offer the option of resending the questionnaire (either by post or email) or to go through the questionnaire over the telephone.

#### Internal pilot

An internal pilot analysis will be conducted following completion of the first six months of planned patient recruitment (starting February 2020). The internal pilot analysis will study whether there has been sufficient site sign-up and patient recruitment, treatment adherence in the conservative oxygen therapy (intervention) group, as well as sufficient separation between the randomised groups in terms of mean measurements of key parameters (SpO<sub>2</sub> and/or FiO<sub>2</sub>). The outcome of this analysis will be presented to the majority-independent Trial Steering Committee who will provide their recommendation as to whether the trial should continue to the Funder (National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme).

#### Independent committees

Both a Trial Steering Committee and a Data Monitoring & Ethics Committee (DMEC) will be convened and will meet regularly during the trial. The DMEC will review available data (including serious adverse events) during the course of the trial. Two interim analyses will be carried out after the recruitment and 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.

#### Timeline

- August 2019 to January 2021 – preparation for start of trial (site sign up and local approvals, production of materials for participating sites, conduct site initiation meetings)
- February 2021 – commence patient recruitment
- May 2021 – start 90 day patient follow-up
- September 2021 – Feasibility assessment
- January 2023 – end patient recruitment
- April 2023 - last patient, last follow-up (end of trial)
- May 2023 to November 2023 - data cleaning, validation, analysis and report writing
- December 2023 - submit Final Report to the Funder (NIHR HTA)

#### **A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?**

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

*Give details of involvement, or if none please justify the absence of involvement.*

We have a strong focus on patient and public involvement (PPI) in the UK-ROX trial. We have a patient representative, with experience of taking part in critical care research, as a co-investigator and member of our Trial Management Group (TMG). They have provided critical input into the study design and development, including development of the deferred consent process and patient facing documents such as the Participant Information Sheets and Consent/Opinion Forms. Elements of the protocol and site training information have also been directly informed by PPI. Our patient representative will be given the opportunity to be involved in the dissemination of findings, in terms of

preparing reports and writing papers, as well as presenting the findings. In addition, at least one independent PPI representative will be a member of the Trial Steering Committee (TSC) which will provide majority-independent oversight of the trial.

#### 4. RISKS AND ETHICAL ISSUES

#### RESEARCH PARTICIPANTS

##### A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- Blood
- Cancer
- Cardiovascular
- Congenital Disorders
- Dementias and Neurodegenerative Diseases
- Diabetes
- Ear
- Eye
- Generic Health Relevance
- Infection
- Inflammatory and Immune System
- Injuries and Accidents
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Oral and Gastrointestinal
- Paediatrics
- Renal and Urogenital
- Reproductive Health and Childbirth
- Respiratory
- Skin
- Stroke

Gender: Male and female participants

Lower age limit: 18 Years

Upper age limit: No upper age limit

##### A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1. Aged  $\geq 18$  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<sub>2</sub>) >0.21) at the time of enrolment

**A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).**

1. Previously randomised into UK-ROX in the last 90 days
2. The clinician considers that one study treatment arm is either indicated or contraindicated.

A data dictionary will contain relevant examples of conditions where clinicians may exclude patients (at their discretion) because conservative oxygen therapy is either indicated or contraindicated (e.g. chronic lung diseases, receiving hyperbaric oxygen, prior bleomycin exposure, carbon monoxide poisoning).

**RESEARCH PROCEDURES, RISKS AND BENEFITS**

**A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.**

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Provide informed consent	1	0	60 minutes	Informed deferred consent will be taken by trained members of the site research team, as authorised by the site PI on the Delegation Log. These staff members will have undergone Good Clinical Practice training and training in the UK-ROX processes and procedures.
Complete follow-up questionnaire	1	0	15 minutes	15% of the total sample size will be invited to complete a follow-up questionnaire at 90-days post-randomisation. A pen and stamped addressed will be provided for ease of return.

**A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.**

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Conservative oxygen therapy (SpO2 target range of 90-93%) - whilst receiving supplemental oxygen	1	1	Variable	All eligible patients will be receiving oxygen therapy at the point of enrolment. For patients randomised to the intervention group, clinical staff will adopt a conservative oxygen therapy strategy, using an SpO2 target range of 90-93%. The lowest concentration of oxygen possible should be administered to maintain the patient's SpO2 at or just above 90%. For patients receiving oxygen, SpO2 should not rise above 93%. Alarms should be set to sound at an SpO2 of 89% and below and 94% and above. Patients randomised to the control group will continue to receive usual oxygen therapy.

**A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?**

Yes  No

**A21. How long do you expect each participant to be in the study in total?**

90 days from randomisation.

**A22. What are the potential risks and burdens for research participants and how will you minimise them?**

*For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.*

Half of the patients enrolled in this trial will be allocated to an intervention group, which will receive treatment that differs from usual care. They will receive oxygen titrated to a lower SpO<sub>2</sub> target than usual care, known as conservative oxygen therapy. Whilst crucial for maintaining normal biological functions in the body, oxygen may also cause harm when administered in excess. The careful balance between too much and too little oxygen is what is being investigated in this study. A recent study evaluating the effect of an SpO<sub>2</sub> target of 91-96% found no difference in harm between that and usual care. Therefore, we do not expect adverse effects to occur in those patients receiving the intervention more so than they would in the control group (usual oxygen therapy). The intervention will also not cause any pain, discomfort, distress, intrusion, inconvenience or change to lifestyle, over and above usual care. Adverse events in the two study groups will be monitored by the DMEC throughout the study.

There are no significant benefits or risks for patients who are allocated to the usual oxygen therapy group. Participating patients will receive usual care whilst in the hospital. All patients, regardless of which treatment group they are in, will be monitored closely for any side-effects or serious adverse events.

One potential perceived burden to patients could be the completion of follow-up questionnaires at 90 days. We have attempted to reduce the burden of this aspect of trial by only following up 15% of the randomised patients. For those 15% of patients, the questionnaires are designed to take no longer than 15 minutes to complete. A self-addressed stamped envelope and pen will be included with questionnaire packs sent to patients for ease of return (and so there is no cost to patients). Information about the follow-up questionnaires will be provided on Patient Information Sheet and Consultee Information Sheet and patients/consultees will be presented with this as an option to consent/agree (or not) for. Our previous studies have achieved response rates ranging 75-80% of critical care survivors, suggesting this aspect is not unduly burdensome.

**A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?**

Yes  No

**A24. What is the potential for benefit to research participants?**

This research aims to improve the care and outcomes of critically ill patients receiving invasive mechanical ventilation and oxygen therapy in ICU. UK-ROX has been designed 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% in the intervention group (conservative oxygen therapy).

We do not currently know if conservative oxygen therapy is beneficial for critically ill patients receiving mechanical ventilation in the ICU, however, if the hypothesis is true and the intervention is found to be clinically effective, participants in the intervention group may benefit from increased survival.

There are no potential significant benefits of taking part for participants in the usual oxygen therapy group, other than the understanding that information from the trial will be used to improve the care of future critically ill patients (although some research suggests improved outcomes for research participants vs non-participants more generally). Full information on potential risks and benefits of participating in UK-ROX will be provided in the Patient Information Sheet and Consultee Information Sheet.

**A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished?** *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

The intervention should continue to ICU discharge or 90 days post-randomisation, whichever comes first.

After discharge or 90 days - oxygen therapy, if required, will be at the discretion of the treating clinician, as per standard care.

**A26. What are the potential risks for the researchers themselves? (if any)**

None.

## RECRUITMENT AND INFORMED CONSENT

*In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.*

**A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?** *For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

All potential participants will be identified by trained staff within the direct healthcare team (local UK-ROX team) when they are admitted to the ICU.

NHS support costs, as agreed with the funder (National Institute for Health Research Health Technology Assessment Programme), should be sought from the Local Clinical Research Network for costs associated with this part of the research.

**A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?**

Yes  No

*Please give details below:*

Patient data which may be identifiable will be reviewed/screened by the local direct healthcare team working on the clinical trial (local UK-ROX team). Eligibility includes the age of the patient.

**A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.** *Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Patient data which may be identifiable will only be reviewed/screened by the local direct healthcare team working on the trial (local UK-ROX team). No identifiable information will be passed to any individual outside of the direct healthcare team until participation is confirmed. All sites will undergo a site initiation meeting where the importance of data security and confidentiality will be outlined.

**A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?**

Yes  No

**A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?**

Yes  No

#### **A29. How and by whom will potential participants first be approached?**

Patients will be screened at ICUs in NHS hospitals by members of the local clinical and/or research teams [local UK-ROX team] (members of the patient's direct healthcare team).

Patients requiring oxygen therapy during mechanical ventilation need this treatment started in a life-threatening emergency and will be unable to provide informed consent at this time due to reduced mental capacity. In life-threatening situations, any delay in commencing treatment could be detrimental to the patient (and also to the scientific validity of the trial – see 'Recruitment and consent' in section A6-2). This makes any attempt to obtain prior informed consent inappropriate. Therefore, once a patient is identified as being eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be enrolled and randomised to receive the assigned treatment immediately. This method of consent is known as 'deferred' or 'retrospective' consent and is recognised in the Mental Capacity Act.

Patients in ICUs are monitored very closely and clinical/research staff working in this setting have extensive experience of assessing capacity in their patients. Once a patient has regained capacity, they will be approached by an authorised member of the site research team for informed deferred consent. This will be done as soon as practically possible (usually within 24 - 48 hours of the patient regaining capacity). [In the interim period, a Personal/Nominated Consultee will be approached to provide their opinion of the patient's wishes regarding participating in the trial]. A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient, data security and confidentiality and the future availability of the trial results.

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; data will be collected from NHS records. Additional options will be provided to cover potential receipt of a follow-up questionnaire (only 15% of patients will be selected to receive the questionnaire) and for anonymised data to be included in future research/shared with approved researchers.

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 time limit will not be set, as the length of time should be determined based on the patient's needs (see A31). 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 can sign on their behalf.

Patients will only be approached by authorised staff members who have received training in UK-ROX processes and procedures and in Good Clinical Practice (GCP). Staff members able to seek consent/opinion in UK-ROX will include doctors, nurses, other allied health professionals and research/clinical trial practitioners, provided that they have been listed and signed off on the local Delegation Log by the Principal Investigator as being adequately trained and capable of undertaking this duty. The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

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 consent to take part in UK-ROX. If they provide verbal consent, they will then be followed up for full written informed consent, in line with the procedures outlined above.

#### **A30-1. Will you obtain informed consent from or on behalf of research participants?**

Yes  No

*If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.*

*If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.*

UK-ROX will use a deferred consent model, developed in conjunction with our Patient and Public Involvement (PPI), and build on the model used in our recent 65 Trial (IRAS: 215503), which also had significant PPI input, carried out in

the same setting. Once a patient has been confirmed as eligible (i.e. they satisfy the inclusion and exclusion criteria), they will be randomised and the randomly allocated treatment commenced as soon as possible.

This model is believed to be the most appropriate as mechanical ventilation is an invasive procedure initiated as a life-saving measure, during an emergency clinical situation. Patients will lack mental capacity due to their medical condition and by virtue of receiving invasive mechanical ventilation at the point that they become eligible for the trial. Any delay in commencing the trial treatment could be detrimental to the patient, as well as to the scientific validity of the trial. 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 opinion of a Personal Consultee, are inappropriate.

If the patient recovers and regains capacity, they will be approached directly by a trained member of the site research team to provide informed deferred consent. In the interim, once the patient's clinical situation is no longer considered emergent, a Personal Consultee will be approached to provide their opinion of the patients wishes with regards to participation in the study. Where the patient has died, and in the situation where there is no Personal Consultee available (or one is available, but does not wish to be involved in the consultation) a Nominated Consultee will be appointed. Where relevant, the patient's consent decision will supersede that of any Consultee.

Where the patient has died, site research teams will be encouraged to consider informing the relatives and close friends of the patient's involvement in the trial (this will likely be a case-by-case decision, in order to reduce potential for distress) but will not prioritise the signing of any forms with them during a very sensitive time.

*If you are not obtaining consent, please explain why not.*

Not applicable.

*Please enclose a copy of the information sheet(s) and consent form(s).*

**A30-2. Will you record informed consent (or advice from consultees) in writing?**

Yes     No

**A31. How long will you allow potential participants to decide whether or not to take part?**

No time limit will be imposed on potential participants to decide whether or not to take part in the study. A principal advantage of the 'deferred' or 'research without prior' consent model is that it allows patients (and/or their Consultees) the necessary time to consider all of the information and to discuss with wider family, friends and clinical and research staff, without the immediate time pressure of the intervention awaiting their decision. Patients and their consultees will be given such time by the trained staff member seeking consent/opinion, to consider all of the information with the aim of confirming their decision prior to hospital discharge. If the patient requires more time, they will be followed up by telephone/post following hospital discharge.

**A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?**

Yes  
 No  
 Not Known

*If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?*

We will include patients who may be part of research protocols as a result of acute or chronic diseases that are not directly related to the need for intensive care.

With respect to ICU studies, the UK-ROX investigators will consider co-enrolment of participants onto other interventional studies where there is no 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. Co-enrolment agreements will be put in place on a case-by-case basis. Co-enrolment will be permitted with observational studies (including those collecting samples) without prior agreement needed.

**A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)**

If the patient (or their Consultee) is unable to adequately understand verbal explanations, detailed written information will be provided. If the patient (or their Consultee) does not understand oral or written information in English, translation services will be used as per routine practice at each of the participating sites. Staff working in ICUs are therefore very experienced at using interpreters frequently, depending on location and case mix, and use of this mechanism will be emphasised in site initiation/training meetings.

We will consider translating patient documentation into a limited number of languages according to demand and budget, however, as we intend to recruit patients from 100 ICUs across the UK, it will not be possible to predict the most common languages in advance.

**A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?**

As per A33-1, all participating hospitals in Wales will have access to a Welsh interpreter.

**A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?**

We are aware of the relevant studies in progress from clinical trial databases that are addressing this or similar research questions. The Chief Investigator will inform both the Trial Steering Committee and the Data Monitoring & Ethics Committee of any relevant new data if it appears.

All information received of any importance will be passed on through the participating sites. Due to the short intervention period (i.e. the intervention is only delivered in the ICU setting), it is highly unlikely information will become available which would be relevant to the patients' continued participation.

**A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.**

- The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- The participant would continue to be included in the study.
- Not applicable – informed consent will not be sought from any participants in this research.
- Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

*Further details:*

It is highly likely that patients will not have mental capacity when enrolled into the study, due to their medical condition and by virtue of receiving invasive mechanical ventilation. There is also a likelihood that patients may lose capacity during the trial. In this situation, capacity may be fluctuating, and this is common in the ICU environment. This has been recognised by the trial team as a distinct possibility and therefore it would be necessary for the participant to continue in the trial.

**Please complete Part B, Section 6, giving further information about arrangements for including adults unable to consent for themselves.**

**CONFIDENTIALITY**

**In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.**

**Storage and use of personal data during the study****A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)**

- Access to medical records by those outside the direct healthcare team
- Access to social care records by those outside the direct social care team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
  - Manual files (includes paper or film)
  - NHS computers
  - Social Care Service computers
  - Home or other personal computers
  - University computers
  - Private company computers
  - Laptop computers

**Further details:**

Members of the UK-ROX trial team from the ICNARC CTU will require access to patient's medical notes during routine trial monitoring visits conducted at the hospital site to ensure the quality of the data collection and consenting procedures.

Identifiable data (e.g. name and contact details) will need to be sent to and stored at ICNARC CTU to enable a follow-up questionnaire to be sent to patients. In addition, further patient identifiable data (e.g. name, date of birth, NHS number and post code) will be required to enable linkage with NHS Digital (or equivalent) for important trial outcome data. All data will be encrypted to an appropriate standard prior to sending from the hospital. Only authorised machines (desktops or laptops) owned by ICNARC will be used by members of the UK-ROX trial team.

The PI and authorised delegated members of the local research team at each site will have access to the link code to the identifying data. ICNARC will also hold the link code for participants in whom consent for follow-up (i.e. questionnaires and data linkage to NHS Digital) is in place.

**A37. Please describe the physical security arrangements for storage of personal data during the study?**

Personal data (e.g. name, NHS number, date of birth) will need to be sent to and stored at ICNARC CTU to enable administration of data linkage and follow-up procedures.

At the ICNARC CTU, personal data is collected on a secure web-based data entry system housed at Exponential-E (a third-party contractor providing services to ICNARC). Exponential-E is a specialist hosting provider and all data security measures are compliant with NHS standards. ICNARC has assessed this supplier as low risk and this is acceptable to ICNARC.

With regards to the ICNARC office based in London, England - physical office security includes a Grade 3 Red Care intruder detection system that has been supplied, installed and is maintained by ADT Fire and Security Plc. All visitors are notified to building security by ICNARC staff in advance.

Data destruction will be carried out in compliance with the UK Policy Framework for Health and Social Care Research and we work with suitably qualified contractors for both electronic and paper record destruction.

**A38. How will you ensure the confidentiality of personal data?** *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

To minimise the use of personal identifiers, participants will be allocated a unique Trial Number and this will be used by the study team in communications with the local research teams at participating sites. ICNARC and the local NHS Trust will hold the link code.

Personal data will only be processed in physical form where absolutely necessary (e.g. when posting a letter to a participant).

ICNARC is registered under the Data Protection Act (Registration number: Z6289325). Confidentiality forms the basis of ICNARC's Information Security Policy. All staff employed by ICNARC sign a contract, which incorporates a confidentiality clause and the consequences of breaching confidentiality are covered in our Disciplinary Procedure. External researchers, temporary staff and contractors are all required to sign a formal confidentiality agreement with ICNARC. Data security and confidentiality are a fixed agenda item at staff meetings for all staff at ICNARC.

**A40. Who will have access to participants' personal data during the study?** *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participant data will be held on a secure web-based data entry system. Access to the secure web-based data entry system in the hospitals will be restricted (by username and password) to trained staff in the hospital, authorised by the site Principal Investigator.

Patients' identifiable data, including full name, date of birth, full address and NHS number will be required at ICNARC. It is necessary to collect this identifiable information as the follow-up questionnaires need to be sent directly to the patient. ICNARC will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified to a third party.

Data will be stored in a secure manner and ICNARC are registered in accordance with the Data Protection Act 2018. Access to participant's personal data will be limited to authorised staff members at the ICNARC CTU (the UK-ROX trial team). The site Principal Investigator will take responsibility for ensuring that study data stored on paper at the site is restricted to authorised personnel only (as per the Delegation Log).

**Storage and use of data after the end of the study****A41. Where will the data generated by the study be analysed and by whom?**

Data will be analysed by appropriately qualified and experienced statisticians at from the ICNARC CTU.

The health economic analyses will be carried out by an appropriately qualified and experienced health economist from the London School of Hygiene and Tropical Medicine (LSHTM).

**A42. Who will have control of and act as the custodian for the data generated by the study?**

	Title	Forename/Initials	Surname
	Mr	Paul	Mouncey
Post	Head of Research / Joint-Chief Investigator		
Qualifications	MSc.		
Work Address	ICNARC CTU Napier House, 24 High Holborn London		
Post Code	WC1V 6AZ		
Work Email	paul.mouncey@icnarc.org		
Work Telephone	02072699277		
Fax			

**A43. How long will personal data be stored or accessed after the study has ended?**

- Less than 3 months  
 3 – 6 months  
 6 – 12 months  
 12 months – 3 years  
 Over 3 years

*If longer than 12 months, please justify:*

ICNARC will keep the identifiable information for no longer than one year after the study has finished (unless participants have agreed otherwise) and the rest of the research data will be kept for up to 15 years.

**A44. For how long will you store research data generated by the study?**

Years: 15

Months: 0

**A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.**

In line with Standard Operating Procedures (SOPs) from the Sponsor (ICNARC) and the ICNARC CTU, all central essential documents will be archived for 15 years after the end of the trial. Once this period has passed, arrangements will be made for its confidential destruction.

**INCENTIVES AND PAYMENTS****A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?**

- Yes  No

**A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?**

- Yes  No

**A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?**

- Yes  No

**NOTIFICATION OF OTHER PROFESSIONALS****A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?**

- Yes  No

*If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.*

## PUBLICATION AND DISSEMINATION

### A50. Will the research be registered on a public database?

*The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.*

Yes  No

*Please give details, or justify if not registering the research.*  
The research will be registered with the ISRCTN Registry.

*Please ensure that you have entered registry reference number(s) in question A5-1.*

### A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- Peer reviewed scientific journals
- Internal report
- Conference presentation
- Publication on website
- Other publication
- Submission to regulatory authorities
- Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- No plans to report or disseminate the results
- Other (please specify)

### A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

It will not be possible to identify any person who has taken part in UK-ROX in any reports or articles. If relevant, extra care will be taken when presenting small numbers in tables. The large number of patients and ICUs taking part in this study will also serve to strengthen the anonymity of individual patients.

### A53. Will you inform participants of the results?

Yes  No

*Please give details of how you will inform participants or justify if not doing so.*

Results will be disseminated to those hospitals who participated in the study, and summarised on the ICNARC website. Participants and their Consultees will be informed in the information sheet as to where they can access results of the study.

## 5. Scientific and Statistical Review

### A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- Independent external review

- Review within a company
- Review within a multi-centre research group
- Review within the Chief Investigator's institution or host organisation
- Review within the research team
- Review by educational supervisor
- Other

*Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:*

The trial has been designed by experts in critical care and research methodology. The trial will be hosted and managed by the specialist ICNARC Clinical Trials Unit (a fully registered UKCRC Clinical Trials Unit).

The trial has been reviewed by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme which commissioned the trial. The review process included anonymous peer review, including by an independent statistician.

*For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.*

*For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.*

**A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:**

- Review by independent statistician commissioned by funder or sponsor
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator's institution
- Review by a statistician within the research team or multi-centre group
- Review by educational supervisor
- Other review by individual with relevant statistical expertise
- No review necessary as only frequencies and associations will be assessed – details of statistical input not required

*In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.*

	Title Forename/Initials Surname
	Anonymous Review
Department	Health Technology Assessment (HTA) programme
Institution	National Institute for Health Research (NIHR)
Work Address	
Post Code	
Telephone	
Fax	
Mobile	
E-mail	

*Please enclose a copy of any available comments or reports from a statistician.*

**A57. What is the primary outcome measure for the study?**

Primary outcome - Clinical evaluation:

- All-cause mortality at 90-days following randomisation.

Primary outcome – economic evaluation:

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

**A58. What are the secondary outcome measures?(if any)**

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, at 90-days.

Economic evaluation secondary outcomes:

- HrQoL, assessed using the EuroQol EQ-5D-5L questionnaire<sup>23</sup> at 90-days
- Resource use and costs at 90-days
- Estimated lifetime incremental cost-effectiveness.

**A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.**

Total UK sample size: 16500

Total international sample size (including UK):

Total in European Economic Area:

*Further details:*

The data collected from the 16,500 patients enrolled into this study will also be included in a global study of 40,000 patients investigating oxygen levels in critically ill patients being treated in ICUs around the world, however, UK-ROX is independently powered to provide results directly relevant to the UK NHS setting.

**A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.**

Based on data from potentially eligible patients in the Case Mix Programme (CMP, the national clinical audit for adult critical care in England, Wales and Northern Ireland) (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 Trial - Lamontagne et al., JAMA 2020), we will recruit a total of 16,500 patients.

**A61. Will participants be allocated to groups at random?**

Yes  No

*If yes, please give details of the intended method of randomisation:*

Randomisation will be performed as soon as possible after confirming eligibility. Patients will be randomised 1:1 to receive conservative (intervention) or usual (control) oxygen therapy 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, acute brain pathologies (excluding hypoxic ischaemic encephalopathy), sepsis and confirmed/highly suspected COVID-19.

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.

**A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by**

**which the data will be evaluated to meet the study objectives.**

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. All analyses will follow the intention to treat principle. Baseline patient characteristics will be compared between the two groups to observe balance and the success of randomisation. These comparisons will not be subject to statistical testing. The delivery of the intervention will be described in detail. Results will be reported in accordance with the CONSORT statement.<sup>26</sup>

Analysis of the primary outcome (90-day all cause mortality) will be performed both adjusted only for stratification variables and then 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 study, 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.

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.

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.

**6. MANAGEMENT OF THE RESEARCH**

**A63. Other key investigators/collaborators.** *Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
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#### A64. Details of research sponsor(s)

##### A64-1. Sponsor

###### Lead Sponsor

Status:  NHS or HSC care organisation  
 Academic  
 Pharmaceutical industry  
 Medical device industry  
 Local Authority  
 Other social care provider (including voluntary sector or private organisation)  
 Other

Commercial status: Non-Commercial

*If Other, please specify: Medical research charity*

###### Contact person

Name of organisation Intensive Care National Audit & Research Centre (ICNARC)  
 Given name Keji  
 Family name Dalemo  
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 Town/city London  
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 Country United Kingdom  
 Telephone 02072699277  
 Fax  
 E-mail ctu@icnarc.org

##### A65. Has external funding for the research been secured?

*Please tick at least one check box.*

- Funding secured from one or more funders  
 External funding application to one or more funders in progress  
 No application for external funding will be made

What type of research project is this?

- Standalone project  
 Project that is part of a programme grant  
 Project that is part of a Centre grant  
 Project that is part of a fellowship/ personal award/ research training award  
 Other

Other – please state:

**Please give details of funding applications.**

Organisation	National Institute for Health Research (NIHR) - Health Technology Assessment (HTA) Programme
Address	NIHR Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House, Enterprise Road, Southampton
Post Code	SO16 7NS
Telephone	02380 595 656
Fax	
Mobile	
Email	hta.funding@nihr.ac.uk

Funding Application Status:  Secured  In progress

Amount: £1,586,886.40

Duration

Years:

Months: 40

*If applicable, please specify the programme/ funding stream:*

What is the funding stream/ programme for this research project?

Health Technology Assessment (HTA) Programme

**A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? Please give details of subcontractors if applicable.**

Yes  No

**A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?**

Yes  No

*Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.*

**A68-1. Give details of the lead NHS R&D contact for this research:**

	Title Forename/Initials Surname
	Dr Gary Minto
Organisation	University Hospitals Plymouth NHS Trust
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Telephone	01752 431776
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

**A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:**

South West Peninsula

For more information, please refer to the question specific guidance.

**A69-1. How long do you expect the study to last in the UK?**

Planned start date: 01/08/2020

Planned end date: 30/11/2023

Total duration:

Years: 3 Months: 3 Days: 30

**A71-1. Is this study?**

Single centre

Multicentre

**A71-2. Where will the research take place? (Tick as appropriate)**

England

Scotland

Wales

Northern Ireland

Other countries in European Economic Area

Total UK sites in study 100

**Does this trial involve countries outside the EU?**

Yes  No

**A72. Which organisations in the UK will host the research? Please indicate the type of organisation by ticking the box and give approximate numbers if known:**

NHS organisations in England 88

<input checked="" type="checkbox"/> NHS organisations in Wales	6
<input type="checkbox"/> NHS organisations in Scotland	
<input checked="" type="checkbox"/> HSC organisations in Northern Ireland	6
<input type="checkbox"/> GP practices in England	
<input type="checkbox"/> GP practices in Wales	
<input type="checkbox"/> GP practices in Scotland	
<input type="checkbox"/> GP practices in Northern Ireland	
<input type="checkbox"/> Joint health and social care agencies (eg community mental health teams)	
<input type="checkbox"/> Local authorities	
<input type="checkbox"/> Phase 1 trial units	
<input type="checkbox"/> Prison establishments	
<input type="checkbox"/> Probation areas	
<input type="checkbox"/> Independent (private or voluntary sector) organisations	
<input type="checkbox"/> Educational establishments	
<input type="checkbox"/> Independent research units	
<input type="checkbox"/> Other (give details)	
Total UK sites in study:	100

**A73-1. Will potential participants be identified through any organisations other than the research sites listed above?**

Yes  No

**A74. What arrangements are in place for monitoring and auditing the conduct of the research?**

## 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 relating to adherence with the protocol will be actively and regularly reviewed centrally and local PIs will be contacted regularly to ensure adherence and the quality of the data.

## 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 study procedures, as required, to ensuring clarity and consistency across sites. The on-site monitoring plan will remain flexible in light of COVID-19 (or equivalent) and where on-site monitoring visits are deemed inappropriate, central monitoring will be enhanced.

**A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?**

In line with Standard Operating Procedures at the ICNARC CTU, a Data Monitoring and Ethics Committee (DMEC) will be convened and will include experienced critical care clinicians and at least one statistician. All members of the DMEC will be independent of both the trial and the Trial Steering Committee (TSC), and will operate under the DAMOCLES Charter. The DMEC will report to the TSC, making recommendations on the continuation, or not, of the

study. Safety and efficacy data will be monitored by the DMEC throughout the trial period.

*If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.*

**A75-2. What are the criteria for electively stopping the trial or other research prematurely?**

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.

**A76. Insurance/ indemnity to meet potential legal liabilities**

*Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

**A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.**

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (NHS sponsors only)
- Other insurance or indemnity arrangements will apply (give details below)

ICNARC holds professional liability insurance (CFC Underwriting Ltd) to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.

*Please enclose a copy of relevant documents.*

**A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.**

*Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- Other insurance or indemnity arrangements will apply (give details below)

ICNARC holds professional liability insurance (CFC Underwriting Ltd) to meet the potential legal liability of the sponsor for harm to participants arising from the design of the research.

*Please enclose a copy of relevant documents.*

**A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?**

*Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.*

- NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

*Please enclose a copy of relevant documents.*

**A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?**

Yes  No

*Please enclose a copy of relevant documents.*

**A78. Could the research lead to the development of a new product/process or the generation of intellectual property?**

Yes  No  Not sure

**B. All research other than CTIMPs**

*In this sub-section, an adult means a person aged 16 or over.*

**B1. What impairing condition(s) will the participants have?**

*The study must be connected to this condition or its treatment.*

Participants will be critically ill patients in ICUs requiring oxygen therapy during invasive mechanical ventilation.

**B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.**

By definition, critically ill patients in ICU are in a critical condition due to their illness and require medical support to help one or more of their organs function. In addition to their illness, many require multiple invasive procedures and treatments (e.g. mechanical ventilation, catheterisation) alongside sedative and analgesic drugs – all of which impact the patient's capacity and ability to communicate and provide consent.

It would not be possible to conduct this type of emergency research in ICUs if confined to adults capable of giving consent, as it is the very patients who are unable to provide consent that the UK-ROX trial seeks to improve the care and outcomes of. It would not be possible to conduct this research in patients able to provide prior informed consent, as such patients would not be representative of the target study population.

**B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?**

Capacity will be assessed by clinical staff working in participating ICUs. Clinical staff working in setting have extensive experience of assessing capacity and working with adults lacking capacity as part of standard ICU care.

**B4. Does the research have the potential to benefit participants who are unable to consent for themselves?**

Yes  No

*If Yes, please indicate the nature of this benefit. You may refer back to your answer to Question A24.*

This research aims to improve the care and outcomes of critically ill patients receiving invasive mechanical ventilation in ICU. UK-ROX has been designed 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% in the intervention group (conservative oxygen therapy).

As stated in A24, we do not currently know if conservative oxygen therapy is beneficial for critically ill patients receiving mechanical ventilation in the ICU, however, if the hypothesis is true and the intervention is found to be clinically effective, participants in the intervention group may benefit from increased survival.

There are no potential significant benefits of taking part for participants in the usual oxygen therapy group, other than the understanding that information from the trial will be used to improve the care of future critically ill patients (although some research suggests improved outcomes for research participants vs non-participants more generally). Full information on potential risks and benefits of participating in UK-ROX will be provided in the Patient Information Sheet and Consultee Information Sheet.

**B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?**

Yes  No

*If Yes, please explain how the research will achieve this:*

This research aims to improve the care and outcomes of critically ill patients in ICUs requiring invasive mechanical ventilation. In the UK, around 30% of all ICU patients receive mechanical ventilation with supplemental oxygen. UK-ROX will therefore contribute to knowledge of treatment and care for this large group of critically ill patients. If the

intervention (conservative oxygen therapy) is found to be clinically and cost-effective, then this knowledge will be used to inform the NHS (and other healthcare systems around the world) regarding the standard care of this patient population. The results of UK-ROX will be actively and widely disseminated to ensure knowledge gained from the trial can influence practice.

**B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?**

Yes  No

*If Yes, please give an assessment below. Highlight any risk, burden or discomfort specific to these participants and say what will be done to minimise it. You may refer back to your answers to Questions A22 and A23.*

As per section A22 - half of the enrolled patients will be allocated to an intervention group, which will receive treatment that differs from usual care. They will receive oxygen titrated to a lower SpO<sub>2</sub> than usual care, known as conservative oxygen therapy. Whilst crucial for maintaining normal biological functions in the body, oxygen may also cause harm when administered in excess. The careful balance between too much and too little oxygen is what is being investigated in this study. A recent study evaluating the effect of an SpO<sub>2</sub> target of 91-96% found no difference in harm between that and usual care. Therefore, we do not expect adverse effects to occur in those patients receiving the intervention more so than they would in the control group (usual oxygen therapy). The intervention will also not cause any pain, discomfort, distress, intrusion, inconvenience or change to lifestyle, over and above usual care.

Adverse events in the two study groups will be monitored by the DMEC throughout the study. There is no significant benefit or risks for patients who are allocated to the usual care group. Participating patients will receive usual care whilst in the hospital. All patients, regardless of which treatment group they are in, will be monitored closely for any side-effects or serious adverse events.

One potential perceived burden to patients could be the completion of follow-up questionnaires at 90 days. This burden is reduced by only aiming to follow-up 15% of enrolled patients.

*Questions B7 and B8 apply to any participants recruited in England and Wales.*

**B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?**

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.

If a patient recovers and regains capacity, they will be approached directly for informed deferred consent. 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 by telephone) as soon as appropriate and practically possible to discuss the trial and to seek their opinion as to the patients' likely wishes and feelings regarding participating in research. 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 by information about why the Personal Consultee has been approached at this stage. 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 research.

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. 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 Personal Consultee 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 research, 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 who has 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 telephone call will be documented and signed by the trained staff member on the Telephone Agreement Form, countersigned by the witness.

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 associated with the conduct of 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 unwilling to be consulted).

*Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.*

**B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?**

Yes  No

*If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or advice from a consultee as soon as practicable thereafter.*

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 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.

Upon patient recovery, they will be approached directly by a trained member of the site research team for informed deferred consent. In the interim, a Personal Consultee will be approached to provide their opinion of the patients wishes and feelings with regards to participating in the study. In the event that the patient has died, or no Personal Consultee is available for consultation, a Nominated Consultee will be appointed and approached.

**Questions B7-2 and B8-2 apply to any participants recruited in Northern Ireland.**

**B7-2. What arrangements will be made to consult a close relative or close friend able to advise on the inclusion of the participant and on their likely wishes?**

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.

If a patient recovers and regains capacity, they will be approached directly for informed deferred consent. 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 by telephone) as soon as appropriate and practically possible to discuss the trial and to seek their opinion as to the patients' likely wishes and feelings regarding participating in research. 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 by information about why the Personal Consultee has been approached at this stage. 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 research.

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. 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 Personal Consultee 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 research, 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 who has 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 telephone call will be documented and signed by the trained staff member on the Telephone Agreement Form, countersigned by the witness.

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 associated with the conduct of 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 unwilling to be consulted).

**B8-2. Is it possible that a participant might need to be treated urgently as part of the research before it is possible to consult with a close relative or close friend?**

Yes     No

*If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants.*

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 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.

Upon patient recovery, they will be approached directly by a trained member of the site research team for informed deferred consent. In the interim, a Personal Consultee will be approached to provide their opinion of the patients wishes and feelings with regards to participating in the study. In the event that the patient has died, or no Personal Consultee is available for consultation, a Nominated Consultee will be appointed and approached.

**B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?**

Critically ill patients in ICUs are monitored very closely due to severity of their illness. Relatives and close friends (Personal Consultees) will continue to be updated and consulted regarding the ongoing care of the patient, including where relevant to ongoing participation in the study, just as they would as part of standard care.

Personal Consultees (and the patient, when appropriate) will be able to withdraw consent for all or specific aspects of the study at any point by informing the clinical/research team caring for the patient. Staff at participating sites will be provided with training in the UK-ROX consent procedures and a Standard Operating Procedure will be followed.

**B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?**

Patients will lack mental capacity due to their medical condition and by virtue of receiving invasive mechanical ventilation at the point that they become eligible for the study. If the patient recovers and regains capacity, they will be approached directly by a trained member of the site research team with verbal and written information about the research.

In the interim, a Personal Consultee will be approached to provide their opinion of the patients wishes and feelings with regards to participating in the study. Where the patient has died, or where no Personal Consultee becomes available for consultation, an independent Nominated Consultee will be appointed and approached in the same way as for the Personal Consultee.

**B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?**

It is likely due to the condition of the patient they will not have capacity when randomised into the study. There is also some likelihood that patients may lose capacity during the study. In this situation, capacity may be fluctuating, and this is common in the critical care environment. This has been recognised by the trial team as a distinct possibility and therefore it would be necessary for the participant to continue in the trial.

The patient's medical condition will be the cause of the incapacity. It is necessary to carry out this research in these patients who may have fluctuating capacity.

**B12-1. What will be the criteria for withdrawal of participants?**

Participants and/or their consultees can request to withdraw from some or all aspects of the study. Declining to receive ongoing treatment in accordance with the study protocol would not constitute a withdraw from the overall trial and such participants would still be included in data collection and follow-up (unless they request otherwise).

**B12-2. Where a participant is recruited urgently, and later withholds their consent or is withdrawn or dies before consent / consultation can take place, what provisions will apply to the study data collected up to that point?**

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 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.

**B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).**

It will be stressed during site initiations to the local site research teams that patient interest and safety is the main consideration when carrying out the protocol. If it is clear the patient objects to any part of the protocol then the treating team should not complete the procedure.

**B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant? *This question applies to England, Wales and Scotland only – please see guidance notes for further information.***

Where patients do not have capacity, advance decision statements will be checked with the Personal or Nominated Consultee. Otherwise if there is any evidence (e.g. in the patient's hospital notes or advanced directive) to indicate that the patient does not wish to be involved in a clinical trial, or is against the specific intervention then the patient will not be randomised.

**PART C: Overview of research sites**

**Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites.** *For further information please refer to guidance.*

Investigator identifier	Research site	Investigator Name

**PART D: Declarations****D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.
3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.
10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
  - ◊ Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
  - ◊ May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
  - ◊ May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
  - ◊ Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
  - ◊ May be sent by email to REC members.
11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.
12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.
13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

**Contact point for publication***(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator
- Sponsor
- Study co-ordinator
- Student
- Other – please give details
- None

**Access to application for training purposes** *(Not applicable for R&D Forms)*

*Optional – please tick as appropriate:*

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr Daniel Martin on 28/10/2020 17:06.

Job Title/Post:            Professor  
Organisation:            University of Plymouth  
Email:                      daniel.martin@plymouth.ac.uk

**D2. Declaration by the sponsor's representative**

*If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.*

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

*Please note: The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Ms Keji Dalemo on 27/10/2020 15:54.

Job Title/Post: CTU Manager  
Organisation: ICNARC  
Email: keji.dalemo@icnarc.org