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Dr Lee Potiphar, Chair
South Central – Oxford C Research Ethics Committee
Health Research Authority
Ground Floor, Temple Quay House
2 The Square
Bristol BS1 6PN

21 December 2020

Dear Dr Potiphar

Study title: **Evaluating the clinical and cost-effectiveness of a conservative approach to oxygen therapy for invasively ventilated adults in intensive care (UK-ROX).**
REC reference: **20/SC/0423**
IRAS number: **288506**

On behalf of the UK-ROX Trial Management Group, I would like to thank the members of the South Central – Oxford C Research Ethics Committee for their detailed review of our application on 27 November 2020 and for issuing favourable ethical opinion with conditions on 8 December 2020.

We have amended and resubmitted the study documentation in response to the Committee's conditions, as detailed below:

#	Ethical Review – Request for Information	Response from the applicant
1	The Committee emphasised that if a participant with capacity consequently loses capacity throughout the study then the individual should either be withdrawn (but use the data already collected) or the advice from a personal/nominated consultee should be sought as the current protocol of participants continuing in the study contradicts the Mental Capacity Act.	This clarification has been added to section 3.4.2 of the Protocol.
2	The Committee noted that only verbal consent will be taken from participants but in order to give consent, participants could communicate this via other methods e.g. through blinking and hand movement.	This clarification has been added to section 3.4.2 of the Protocol.
3	The Committee requested that the opt-out form for personal consultees is removed from the study as, if a personal consultee cannot be sought, then, according to the Mental Capacity Act, a nominated consultee should be pursued.	References to this procedure have been removed from the Protocol. The 'opt-out form for personal consultees' and Postal Personal Consultee Opinion Form have been removed from the study documents.

4	The Committee requested it is made explicit in the patient follow-up letter after the section "If you **do not wish** to fill in the questionnaire, then please tick the box on the front of the questionnaire and return it to us using the stamped, addressed envelope provided" that if the individual does not respond to the letter then they will continue to be included in the study.	This clarification has been added to the patient follow-up letter.
5	The Committee requested the Participant Information Sheet format is amended so the information is provided in one column rather than two.	We originally developed the Participant Information Sheets using two formats - one using a one-column layout and, the other, a two-column layout. The two-column layout was informed by examples promoted on the HRA Consent and Participant Information Guidance website (http://www.hra-decisiontools.org.uk/consent/examples.html). Feedback form our Patient and Public Involvement (PPI) co-investigator indicated that the two-column format was much more readable and visually appealing and hence this format was submitted. In light of our PPI feedback, we have decided to keep this format. We have added additional vertical lines and improved spacing to help improve the flow of the information. We will, however, continue to seek feedback in the early stages of the trial and amend the documents if this what feedback indicates would be beneficial.

We also respond to the HRA/HRCW assessment queries, as follows:

#	**HRA and HCRW assessment - Further Information Required**	**Response from the applicant**
1	As discussed via email, the list of sites and Principal Investigators that have been identified can be provided Cover Letter/as part of the response.	Please see Appendix 1 of this letter for our current list of sites and Principal Investigators.

2	It has been noted that a Consultee will be approached for participants who pass away before consent can be obtained. Please confirm that no further data will be collected from the participant after their passing. Note that if identifiable data of the deceased is accessed outside the care team, consent can only be given by a personal representative or someone who has a claim resulting from their death (https://www.nhs.uk/common-health-questions/nhs-services-and-treatments/can-i-access-the-medical-records-health-records-of-someone-who-has-died/). Alternatively, a submission to the CAG may be required (https://www.hra.nhs.uk/about-us/committees-and-services/confidentiality-advisory-group/guidance-confidentiality-advisory-group-applicants/).	Considering the anticipated relatively high mortality rate expected in this patient population, it is essential to monitor safety up to the final study end points for all trial participants, to ensure unbiased results. Where relevant, data will only be collected on events occurring up to, and including, the date/time of death (the final trial end point).
3	All Consent/Declaration Forms [Study Title] Add the full study title to the documents (this can be in the footer).	The study title has been added to the Consent/Opinion Forms.
4	All Information Sheets [Page 5, Harm] The Sponsor's insurance arrangements should be briefly explained.	These details have been added to the Information Sheets.
5	Thank you for submitting the insurance document. The policy does not appear to cover what we would usually expect. Please send confirmation that you have “Public Liability” and/or “Clinical Trials Liability” in place.	I can confirm that our insurance policy will be extended to include Clinical Trials Liability for this trial prior to the start of patient recruitment.

We have also taken this opportunity to make the following changes to the protocol:

- We have added ‘*Currently receiving extracorporeal membrane oxygenation (ECMO)*’ as an exclusion criteria. This has been added because oxygen therapy is typically managed different during ECMO;
- We have removed reference to stratifying the randomisation allocation by COVID-19 status; and
- minor administrative changes to the Protocol.

Please do let me know if there is any further information or clarification that you or the Committee require.

I look forward to hearing from you.

Yours sincerely

Mr Alvin Richards-Belle
Trial Manager

Copy to: Professor Daniel Martin OBE, Chief Investigator
Mr Paul Mouncey, Joint-Chief Investigator
Ms Keji Dalemo, Sponsor Contact
Maeve Ip Groot Bluemink, Health Research Authority contact

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UK-ROX Trial Protocol v1.1, 14 December 2020 (tracked and clean versions)
Patient follow-up letter v1.1, 14 December 2020 (tracked and clean versions)
Consent Form v1.0 20 October 2020 (with full study name added to footer)
Nominated Consultee Opinion Form v1.0 20 October 2020 (with full study name added to footer)
Personal Consultee Opinion Form v1.0 20 October 2020 (with full study name added to footer)
Postal Consent Form v1.0 20 October 2020 (with full study name added to footer)
Telephone Consent Form v1.0 20 October 2020 (with full study name added to footer)
Telephone Personal Consultee Opinion Form v1.0 20 October 2020 (with full study name added to footer)
Patient Information Sheet v1.1, 14 December 2020 (tracked and clean versions)
Nominated Consultee Information Sheet v1.1, 14 December 2020 (tracked and clean versions)
Personal Consultee Information Sheet v1.1, 14 December 2020 (tracked and clean versions)
Final Schedule of Events Cost Attribution Template (SoECAT) validated 2 December 2020

Appendix 1 – List of participating sites and Principal Investigators (PIs)

Bristol Royal Infirmary (University Hospitals Bristol and Weston NHS Foundation Trust)
PI: Dr Jeremy Bewley (Jeremy.Bewley@uhbw.nhs.uk)

Chelsea and Westminster Hospital (Chelsea and Westminster NHS Foundation Trust)
PI: Dr Marcela P Vizcaychipi (marcela.vizcaychipi@chelwest.nhs.uk)

Cumberland Infirmary (North Cumbria Integrated Care NHS Foundation Trust)
PI: Dr Tim Smith (tim.smith@ncic.nhs.uk)

Derriford Hospital (University Hospital Plymouth NHS Trust)
PI: Dr Julian Lentaigne (j.lentaigne@nhs.net)

Dorset County Hospital (Dorset County Hospital NHS Foundation Trust)
PI: Dr Mark Pulletz (mark.pulletz@dchft.nhs.uk)

Guy's Hospital (Guy's & St Thomas' NHS Foundation Trust)
PI: Dr Duncan Wyncoll (duncan.wyncoll@gstt.nhs.uk)

Glangwili General Hospital (Hywel Dda University Health Board NHS Trust)
PI: Dr Igor Otahal (igor.otahal@wales.nhs.uk)

Hull Royal Infirmary (Hull University Teaching Hospitals NHS Trust)
PI: Dr Andrew Gratrix (andrew.gratrix@hey.nhs.uk)

The James Cook University Hospital (South Tees Hospitals NHS Foundation Trust)
PI: Professor Stephen Bonner (stephen.bonner@nhs.net)

Kings Mill Hospital (Sherwood Forest Hospitals NHS Foundation Trust)
PI: Dr Valli Ratnam (valli.ratnam@nhs.net)

Leicester Royal Infirmary (University Hospitals of Leicester NHS Trust)
PI: Dr Christopher Hebbes (christopher.p.hebbes@uhl-tr.nhs.uk)

Maidstone Hospital (Maidstone and Tunbridge Wells NHS Trust)
PI: Dr David Golden (david.golden@nhs.net)

Pinderfields Hospital (Mid Yorkshire NHS Trust)
PI: Dr Brendan Sloan (brendan.sloan1@nhs.net)

Poole Hospital (University Hospitals Dorset NHS Foundation Trust)
PI: Dr Henrik Reschreiter (henrik.reschreiter@uhd.nhs.uk)

Queen Alexandra Hospital (Portsmouth Hospitals University NHS Trust)
PI: Dr David Pogson (david.pogson@porthosp.nhs.uk)

Queen Elizabeth Hospital Woolwich (Lewisham and Greenwich NHS Trust)
PI: Dr Jawad Subhani (jawad.subhani@nhs.net)

The Queen Elizabeth Hospital King's Lynn (The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust)
PI: Dr Peter Young (peteryoung101@googlemail.com)

Queens Hospital Burton (University Hospital of Derby and Burton NHS Foundation Trust)
PI: Dr Amro Katary (Amro.katary@nhs.net)

Queens Medical Centre (Nottingham University Hospitals NHS Trust)
PI: Dr Daniel Harvey (daniel.harvey@nuh.nhs.uk)

Royal Blackburn Teaching Hospital (East Lancashire Hospitals NHS Trust)
PI: Dr Nick Truman (nicholas.truman@elht.nhs.uk)

Royal Bournemouth Hospital (University Hospitals Dorset NHS Foundation Trust)
PI: Dr Nigel Chee (nigel.chee@uhd.nhs.uk)

Royal Cornwall Hospital (Royal Cornwall Hospital Trusts)
PI: Dr Mike Spivey (michaelspivey@nhs.net)

Royal Free Hospital (Royal Free London NHS Foundation Trust)
PI: Dr Mark De Neef (mark.deneef@nhs.net)

Royal Oldham Hospital (Pennine Acute Hospitals NHS Trust)
PI: Dr Redmond Tully (redmond.tully@pat.nhs.uk)

Royal Papworth Hospital (Royal Papworth Hospital NHS Foundation Trust)
PI: Dr Alain Vuylsteke (a.vuylsteke@nhs.net)

Scarborough General Hospital (York Teaching Hospital NHS Foundation Trust)
PI: Dr Philip Dickinson (phillip.dickinson@york.nhs.uk)

St Richard's Hospital (Western Sussex Hospitals NHS Foundation Trust)
PI: Dr Mike Margarson (m.margarson@nhs.net)

St Thomas' Hospital (Guy's & St Thomas' NHS Foundation Trust)
PI: Dr Duncan Wyncoll (duncan.wyncoll@gstt.nhs.uk)

Sunderland Royal Hospital (South Tyneside and Sunderland NHS Foundation Trust)
PI: Dr Anthony Rostron (anthony.rostron@nhs.net)

Tunbridge Wells Hospital (Maidstone and Tunbridge Wells NHS Trust)
PI: Dr David Golden (david.golden@nhs.net)

University Hospital of Wales (Cardiff and Vale University Health Board)
PI: Dr Matt Morgan (mattmorgan@me.com)

West Suffolk Hospital (West Suffolk NHS Foundation Trust)
PI: Dr Vijayakumar Gopal (Vijayakumar.Gopal@wsh.nhs.uk)

York Hospital (York Teaching Hospital NHS Foundation Trust)
PI: Dr George Priestley (george.priestley@york.nhs.uk)