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Dr Lee Potiphar, Chair
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19 March 2021

Dear Dr Potiphar

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|---|---|
| **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** |

I wish to seek a substantial amendment for the above study. Following review by the UK-ROX Trial Management Group, this proposed amendment is to change the implementation of the conservative oxygen therapy intervention. Previously, the intervention was described as "conservative oxygen therapy [$SpO_2$ target range of 90-93%]." Now, the intervention is described as "conservative oxygen therapy [$SpO_2$ target of 90 (±2)%)]". The rationale for this change is detailed below.

Over the last 12 months, intensive care units (ICUs) in the UK have been overwhelmed with patients suffering from COVID-19, an illness defined by hypoxaemia. During that time, healthcare providers have been required to re-evaluate their approach to managing patients with life-threatening acute hypoxaemic respiratory failure. Now that the second wave of the pandemic is subsiding in UK hospitals, we felt that it was imperative to re-evaluate clinical practice and current views on oxygen therapy in ICU. Furthermore, as the start of the trial was delayed due to the pandemic, we have also reviewed the current evidence-base in this area in order to ensure that the UK-ROX trial remains relevant.

1. <u>COVID-19 and the UK-ROX trial</u>

During the COVID-19 pandemic, concerns were raised in the UK about oxygen supply within hospitals, as a result of the physical limitation of gas flow within hospital pipework infrastructures. In response to this, national guidance was published recommending that the British Thoracic Society's recommended oxygen saturation ($SpO_2$) target for an acutely unwell patient of 94-98% be modified to a target of 92-96% in all adult patients.[1] This guidance also specified that in hospitals where oxygen flow was limited, this could be further modified in ICUs to an $SpO_2$ target of 90-94%, if deemed clinically appropriate. In practice, many ICUs specified even lower $SpO_2$ targets, commonly 88-92%. To the best of our knowledge, using these conservative oxygenation targets during the pandemic did not form part of any randomised trial, so we remain uncertain as to whether these lower $SpO_2$ targets are safe or effective in reducing mortality. These targets were initiated in response to a nationwide crisis in delivering oxygen effectively, not because they were deemed beneficial to patients. Thus, whilst clinicians became familiar and comfortable with conservative oxygen targets, the evidence base did not advance.

2. Evidence review

In January 2021, the largest study in this field to date (the HOT-ICU trial) reported that, in 2,928 adults with acute hypoxaemic respiratory failure, conservative oxygen therapy (a partial pressure of oxygen ($PaO_2$) target of 8.0 kPa, versus 12.0 kPa) did *not* significantly affect 90 day mortality.[2] In light of this new evidence we conducted a rapid, trial-level meta-analysis to include this study and to establish the combined best evidence for conservative oxygen therapy in critically ill patients.[2-7] The meta-analysis yielded a risk ratio for 90-day mortality (except for Girardis et al 2016, where mortality was only reported to hospital discharge) of 0.99 (95% confidence intervals: 0.87 to 1.14). Thus, the evidence published to date continues to support clinical equipoise and the need for a large-scale study to answer whether conservative oxygen therapy is effective in reducing mortality in mechanically ventilated ICU patients. We have also been in direct contact with the authors of the HOT-ICU trial to discuss the difficulties they encountered during the study, in particular, compliance to the study intervention targets. As with other studies using physiological parameters as part of an intervention, human nature is to err towards the end of the target which is felt to be closest to usual practice, in the case of oxygenation, higher rather than lower $SpO_2$ or $PaO_2$ values.

Given this new trial information and considering that clinicians have expressed they are now more comfortable with the use of conservative oxygen therapy, we have reconsidered our current intervention $SpO_2$ target of 90-93%. The matter has been discussed at Trial Management Group meetings which included two important members of the investigator team:

1. Professor Mike Grocott, who was part of the NHS England team that determined the pandemic $SpO_2$ targets mentioned above.
2. Dr Ronan O'Driscoll, lead author of the British Thoracic Society guideline for oxygen use in adults in healthcare and emergency settings.

The matter was then further discussed with the chairs of the Trial Steering Committee and Data Monitoring and Ethics Committee. The conclusion of these discussions was that we would like to request that the intervention for the UK-ROX trial be altered to an optimal $SpO_2$ target of 90%, with a 2% leeway in both directions (higher and lower) to allow an overall range of 88-92% (i.e. "$SpO_2$ target of 90 (±2)%)." The key reasons for requesting this alteration are:

- Our concern that previous oxygenation trials have struggled to achieve their intervention targets so, if we remained with a target of 90-93%, the reality is that the measured $SpO_2$ may end up higher than this, threatening adequate oxygenation separation between the intervention and comparator groups.
- Sites have already expressed their desire to target $SpO_2$ values lower than 90%, therefore giving them the option to be within a range of 88-92% may encourage uptake of the trial at the greatest number of sites.
- Given that hospitals have recently been threatened by a shortage of oxygen, it has never been more important to evaluate conservative oxygen therapy if it is to be advocated by NHS England and NICE when this occurs.
- Recent trial data supports clinical equipoise and the need to fully evaluate conservate oxygen therapy.

We have also discussed this with our Patient and Public Involvement co-investigator who is fully supportive of this change and has provided valuable input into the revision of the relevant patient-facing documents.

Amended documents

In light of the above, the Trial Protocol and patient-facing documents that reference the conservative oxygen therapy target have been amended. We have also taken this opportunity to make the following changes to the protocol:

- The start of the internal pilot has been changed from month 7 to month 10 (of the grant timeline), following approval from the funder.
- The definition of the end of the trial was corrected from “last patient, last follow-up” to “last patient, last 90-day follow-up.”
- Other minor administrative changes and corrections.

Please do not hesitate to get in touch if you require any further information to consider this substantial amendment.

I look forward to hearing from you.

Yours sincerely

Professor Daniel Martin OBE
Chief Investigator

Copy to: Mr Paul Mouncey, Joint-Chief Investigator
Ms Keji Dalemo, Sponsor Contact
Maeve Groot Bluemink, Health Research Authority Contact

**Enc.**
UK-ROX Trial Protocol v1.2, 19 March 2021 (tracked and clean versions)
Patient Information Sheet v1.2, 19 March 2021 (tracked and clean versions)
Nominated Consultee Information Sheet v1.2, 19 March 2021 (tracked and clean versions)
Personal Consultee Information Sheet v1.2, 19 March 2021 (tracked and clean versions)
Information Leaflet v1.1, 19 March 2021 (tracked and clean versions)
Patient Newsletter v1.1, 19 March 2021 (tracked and clean versions)

**References**


1. NHS England, *Specialty guides for patient management during the coronavirus pandemic. Clinical guide for the optimal use of oxygen therapy during the coronavirus pandemic.* 2020.
2. Schjørring, O.L., et al., *Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure.* N Engl J Med, 2021.
3. Barrot, L., et al., *Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome.* New England Journal of Medicine, 2020. **382**(11): p. 999-1008.
4. Mackle, D., et al., *Conservative Oxygen Therapy during Mechanical Ventilation in the ICU.* N Engl J Med, 2020. **382**(11): p. 989-998.
5. Asfar, P., et al., *Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial.* Lancet Respir Med, 2017. **5**(3): p. 180-190.
6. Girardis, M., et al., *Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial.* Jama, 2016. **316**(15): p. 1583-1589.
7. Panwar, R., et al., *Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial.* Am J Respir Crit Care Med, 2016. **193**(1): p. 43-51.