UK-ROX: United Kingdom Intensive Care Unit Randomised Trial Comparing Two Approaches to Oxygen Therapy

Overview

Background

The optimal oxygen saturation (SpO₂) target to guide oxygen therapy in mechanically ventilated patients is not known. Both too much (hyperoxaemia) and too little oxygen (hypoxaemia) may lead to adverse events and increase the risk of death. Establishing the balance between these risks that leads to the best clinical outcomes is fundamental to the practice of intensive care medicine.

Concerns about the harm that may be caused by hypoxaemia has led to a tendency to provide more oxygen to patients than may be required, resulting in hyperoxaemia. A systematic review and meta-analysis of acutely unwell patients found that giving less oxygen (compared to ‘liberal’), to achieve a lower than normal SpO₂ target (‘conservative’ oxygen therapy), resulted in lower mortality. Guidance published following this suggests avoiding an SpO₂ of >96% in these acutely unwell patients. Randomised trials have shown mixed results when comparing conservative to ‘liberal’ or usual oxygen therapy in mechanically ventilated patients on an intensive care unit (ICU), leaving a knowledge gap that requires urgent attention.

Our research question: in mechanically ventilated, adult admissions to ICU, is conservative oxygen therapy superior to usual oxygen therapy in terms of all-cause mortality at 90 days (clinical effectiveness) and incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 90 days (cost-effectiveness)?

Aim

To evaluate the clinical and cost-effectiveness of conservative oxygen therapy (an SpO₂ target of 90 (±2)%), as compared with usual care, in mechanically ventilated ICU patients in the UK.

Design

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

Primary objectives
To evaluate the effect of conservative versus usual oxygen therapy on:

- 90-day all-cause mortality (clinical effectiveness)
- Incremental costs, quality-adjusted life years and net monetary benefit at 90 days (cost-effectiveness).

Secondary objectives
To evaluate the effect of conservative versus usual oxygen therapy on:

- 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
- Resource use and costs at 90 days
- Estimated lifetime incremental cost-effectiveness.

Site eligibility criteria

- Active participation in the Case Mix Programme (CMP) or equivalent national clinical audit
- Identify a local Principal Investigator and sub/associate Principal Investigator
- Identify a UK-ROX research nurse responsible for day-to-day local trial coordination
- Agree to incorporate UK-ROX into routine critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations and ensure adherence to the protocol
- Agree to randomise, where possible, all eligible patients and maintain a Screening Log
- Agree to data collection requirements.

Patient eligibility criteria

Inclusion criteria
1. Aged ≥18 years
2. Receiving invasive mechanical ventilation in the ICU following an unplanned ICU admission (i.e. not admitted after an elective procedure) OR invasive mechanical ventilation started in the ICU (i.e. the patient was intubated in the ICU)
3. Receiving supplemental oxygen (fractional inspired oxygen concentration (FiO₂) >0.21) at the time of enrolment.

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

Patients must be enrolled within 12 hours of fulfilling the eligibility criteria.
The trial is being designed in such a way that we would intend recruitment to continue in the face of an increase in COVID-19 admissions (i.e. recruiting both eligible COVID-19 and non-COVID-19 patients).

Co-enrolment will be permitted with observational studies (including those collecting samples) without prior agreement needed. Co-enrolment agreements will be put in place on a case-by-case basis with other interventional trials.

Sample size

- 16,500 patients
- 100 NHS adult intensive care units
- 24-month recruitment period

Randomisation

- Patients will be randomised 1:1 between the intervention and control groups using a deferred consent model.

Intervention group: Conservative oxygen therapy (SpO₂ target of 90 (±2)% whilst receiving oxygen)

- The lowest concentration of oxygen possible should be administered to maintain the patient’s SpO₂ at 90 (±2)%.
- For patients receiving oxygen, SpO₂ should not rise above 92%
- Alarms should be set to sound at an SpO₂ of 88% and below and 92% 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
- All other care will be at the discretion of the treating clinical team.

Control group: Usual care

- All care will be at the discretion of the treating clinical team
- An upper SpO₂ alarm must not be used.

Data collection

To ensure an efficient design, data collection is nested within the Case Mix Programme and will utilise additional routinely collected data from other national NHS sources.

For 14,000 (85%) patients, only a minimal, basic level of primary data collection at the time of randomisation will be conducted. An enhanced level of data collection will be on 2,500 (15%) patients. The patients for the “enhanced” data collection will be the first 10 patients recruited from each site, plus retrospectively randomly selected patients, with a view to monitoring adherence.
### Assessment for eligibility

**Meet all Inclusion criteria:**

- Aged ≥18 years
- Receiving invasive mechanical ventilation in the ICU following an unplanned ICU admission OR invasive mechanical ventilation started in the ICU
- Receiving supplemental oxygen (FiO2 >0.21) at the time of enrolment

**And none of the exclusion criteria:**

- Previously randomised into UK-ROX in the last 90 days
- Currently receiving extracorporeal membrane oxygenation (ECMO)
- The clinician considers that one study treatment arm is either indicated or contraindicated

---

**Randomisation (n = 16,500)**

**Intervention (n = 8,250)**

Conservative oxygen therapy

Lowest concentration of supplemental oxygen to maintain an SpO2 range of 90 (±2)%

**Control (n = 8,520)**

Usual oxygen therapy

---

**Collection of patient identifiers for data linkage**

- Intervention: n = 7,000, 85%
- Control: n = 7,000, 85%

**Collection of patient identifiers and detailed in-patient data for adherence**

- Intervention: n = 1,250, 15%
- Control: n = 1,250, 15%

**Questionnaire follow up at 90 days**

---

**Data linkage between Case Mix Programme, national death records and Hospital Episode Statistics**
**Trial Management and Investigator team**

| **Chief Investigators** | Professor Daniel Martin, University of Plymouth  
Mr Paul Mouncey, ICNARC |
|-------------------------|-------------------------------------------------|
| **Co-Investigators**    | Dr James Doidge, ICNARC  
Dr Douglas Gould, ICNARC  
Dr Paul Young, Wellington Regional Hospital  
Dr Ronan O’Driscoll, Salford Royal NHS Foundation Trust  
Dr Zia Sadique, London School of Hygiene and Tropical Medicine  
Mr Alvin Richards-Belle, ICNARC  
Mrs Joanne Jones, Maidstone and Tunbridge Wells NHS Trust  
Mrs Miriam Davey, Maidstone and Tunbridge Wells NHS Trust  
Professor David Harrison, ICNARC  
Professor Kathryn Rowan, ICNARC  
Professor Michael Grocott, University of Southampton |
| **Trial Management**    | ICNARC Clinical Trials Unit |