Intensive Care Unit Randomised Trial Comparing Two Approaches to Oxygen Therapy

Site Initiation Visit

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Sponsor: ICNARC (01/10/20)

Chief Investigators: Prof Daniel Martin & Mr Paul Mouncey
Agenda

- Background and trial design
- Patient flow
Background

• Oxygen is the commonest drug administered to patients on ICU
• Approx. 55,000 patients per year receive mechanical ventilation with supplemental oxygen in NHS ICUs
• Whilst severe hypoxaemia can be harmful, the administration of excessive oxygen may also be harmful
• Traditionally we have given *more* (rather than less) oxygen to avoid hypoxaemia
• We do not know what the optimal amount of oxygen to give to patients is, or what their optimal oxygenation level should be
Background

• High concentration oxygen is thought to be harmful to the lungs and induce an inflammatory response

• Retrospective studies have linked hyperoxaemia to worse clinical outcomes

• *Conservative oxygen therapy* (or permissive hypoxaemia) is the purposeful administration of less oxygen than usual to patients, to achieve lower than normal arterial oxygenation levels ($SpO_2 / PaO_2$)
Aim

- To evaluate the clinical and cost-effectiveness of conservative oxygen therapy for mechanically ventilated adult patients in ICU

Research question

Population: In adults receiving mechanical ventilation and supplemental oxygen in ICU
Intervention: is conservative oxygen therapy superior to
Comparator: usual oxygen therapy
Outcome: in terms of 90-day all-cause mortality?
Trial design

- Large-scale, multi-centre, data-enabled, registry-embedded, RCT with an internal pilot and integrated economic evaluation
- 16,500 patients (randomised 1:1)
  - Provides 90% power to detect a 2.5% absolute risk reduction in 90-day mortality (from 37% to 34.5%), with allowances for missing data
  - Recruited from approx. 100 ICUs
  - 24-month recruitment period
Agenda

- Background and trial design
- Patient flow
Patient flow

Screening

Randomisation

Conversative oxygen therapy

Usual oxygen therapy

Consent

Follow-up

Safety monitoring

Data collection
Eligibility

- **Inclusion criteria**
  - Aged ≥18 years
  - Receiving invasive mechanical ventilation following an unplanned ICU admission OR invasive mechanical ventilation started in the ICU
  - $\text{FiO}_2 > 0.21$ at time of randomisation

- **Exclusion criteria**
  - Previously randomised to UK-ROX in last 90 days
  - Currently receiving ECMO
  - The treating clinician considers that one study treatment arm is either indicated or contraindicated

- Patients must be randomised within **12 hours** of starting invasive mechanical ventilation in ICU
Screening & randomising

- Screen all patients receiving invasive mechanical ventilation in ICU
  - Eligible if intubated at ICU admission OR later during the ICU stay

- Aiming to embed screening within routine clinical practice
- Timely randomisation essential (12-hour window)
- Simple trial procedures
- Coverage for out-of-hours randomisations
  - clinical staff training and engagement
### Screening Tool (optional)

#### Screening Tool

<table>
<thead>
<tr>
<th>Hospital number</th>
<th>Aged ≥18 years? (Y/N)</th>
<th>Datetime started invasive mechanical ventilation</th>
<th>Screened within 12 hours of starting invasive mechanical ventilation? (Y/N)</th>
<th>Eligibility confirmed by Name of staff</th>
<th>If randomised Trial Number</th>
<th>If not randomised Provide reason</th>
</tr>
</thead>
</table>

- If all Yes, then review exclusion criteria and complete Randomisation Form if all eligibility criteria are met.

### Exclusion criteria
- Previously randomised into UK-ROX in the last 90 days
- Currently receiving ECMO
- The treating clinician considers that one study treatment arm is either indicated or contraindicated

### Unsure if a patient is eligible? Contact:
- Your Principal Investigator or research team for assistance
- ICNARC CTU: 020 7269 9277 or uk.rox@icnarc.org

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See SOP 003
Co-enrolment

- Observational studies (including those collecting samples)
  - Permitted without prior agreement

- Interventional studies
  - Decided case-by-case
  - Agreement in place with:
    - A2B
    - EFFORT
    - REMAP-CAP
    - VITDALIZE UK
    - VACIRiSS
    - STRESS-L
    - ADAPT-SEPSIS
    - RECOVERY
    - BLING III

See SOP 004
Patient flow

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Data collection
Randomisation

- Dedicated 24/7 randomisation service
- Telephone randomisation
  - Dial: 020 3384 6368
  - Study number: 7102
  - Your investigator number will be assigned
- Web randomisation
  - Email uk-rox@icnarc.org to request an account
  - Can use generic/group or individual email addresses

- Trial training required to randomise (Training Log)
  - GCP training not required
### How to randomise

#### Details required by randomisation service
- Confirmation of eligibility
- Key baseline data

#### Confirmation of randomisation

#### Sign off by trained staff member
Randomisation

- Auto-generated randomisation notification emails
  - Email [uk-rox@icnarc.org](mailto:uk-rox@icnarc.org) to add recipients

- Errors
  - Once randomised, patient is in trial and included in analysis - consent and data collection must be carried out per protocol
  - If patient accidentally randomised twice, use **first** randomisation
    - Check email notification if unsure of the status of a randomisation (or contact local team/ICNARC CTU)
    - **Do not** re-use the second randomisation details
Patient flow

1. Screening
2. Randomisation
3. Consent
4. Follow-up

- Conversative oxygen therapy
- Usual oxygen therapy

Additional processes:
- Safety monitoring
- Data collection

Site Initiation Visit
Intervention period

- Begins immediately following randomisation

- The interventions remain the same once a patient is extubated, regardless of the modality by which they receive oxygen therapy

- The interventions should be continued until ICU discharge or 90 days after randomisation, whichever is sooner
  - If readmitted to ICU within the 90 days, the intervention should be recommenced
Conservative oxygen therapy

- The **lowest concentration of oxygen possible** should be administered to maintain the patient’s $\text{SpO}_2$ at $90(\pm 2)\%$

- For patients receiving oxygen, $\text{SpO}_2$ should not rise above $92\%$ (monitor alarm set to 93%)

- $\text{SpO}_2$ should not fall lower than $88\%$
Conservative oxygen therapy

CONSERVATIVE OXYGEN THERAPY
When receiving oxygen

Set upper alarm to prevent an SpO₂ > 92%
Reduce FiO₂ until SpO₂ is 90%
Set lower alarm to prevent an SpO₂ < 88%

* If SpO₂ is > 92% despite an FiO₂ of 0.21, the upper alarm will need to be removed

See SOP 005
Conservative oxygen therapy

- When a patient is not receiving additional oxygen, a higher SpO₂ alarm should not be set
- Continue to monitor SpO₂
- If additional oxygen is required again, revert to the algorithm for patients receiving oxygen
Conservative oxygen therapy

- Intervention 90±2% (88-92%)

- This is the intervention we trialled in our UK feasibility study

- Every RCT to date has selected a different intervention target

- We originally selected 90—94% for UK-ROX but have reduced it to 88-92% in line with feedback from centres and following experiences during the COVID-19 pandemic
Protocol deviation

- Trigger to identify potential deviations:
  - where SpO₂ remains above 92% for three consecutive hours and FiO₂ is not reduced or at the lower limit of 0.21
- Sites contacted to find out reasons why oxygen was not reduced
  - Important that reasons are documented locally
Training

• Ensure staff are aware of trial and that they may be managing intervention group patients
  - Including temporary/bank/agency staff
• Ensure bedside staff are confident in titrating $F_iO_2$ to an $SpO_2$ target of 90 ($\pm 2$)%
• Ensure alarms are set appropriately and $SpO_2$ targets handed over to subsequent shifts
• Discussion point at ward rounds
• Use of electronic patient record to monitor $SpO_2$ values and prompt titration of $FiO_2$?
• Use stickers/labels for intervention group patients
Patient flow

Screening

Randomisation

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Usual oxygen therapy

Consent

Follow-up

Safety monitoring

Data collection
Usual oxygen therapy

- Defined by local practice, determined by treating clinician
- Chosen SpO$_2$ targets should be documented daily
- A lower limit alarm can be set at the discretion of the treating clinician
- An upper SpO$_2$ alarm must not be used
- Research staff should avoid interactions that may influence usual care

See SOP 006
Patient flow

Screening

Randomisation

Conversative oxygen therapy

Usual oxygen therapy

Consent

Follow-up

Safety monitoring

Data collection
Research Without Prior Consent

- Patients will lack capacity at time of randomisation
- Emergency waiver of consent granted by REC (Mental Capacity Act)

- Once patient’s medical situation is considered no longer an emergency, the consent procedures should begin
  - Consent sought after randomisation by GCP-trained team member
  - Expected to be within 24-48 hours of randomisation

- Posters and leaflets publicly available
Patient flow

Screening

Randomisation

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Follow-up

Conversative oxygen therapy

Usual oxygen therapy

Data collection

Safety monitoring
Safety monitoring

- Monitor safety between randomisation and ICU discharge or 90 days (whichever comes first)*
- Serious Adverse Events (SAEs) reported to ICNARC CTU:

<table>
<thead>
<tr>
<th>Expected Events</th>
<th>Unexpected Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Report all occurrences assessed as ‘severe’ or ‘life-threatening’ (SAEs):</td>
<td>• Report only if considered to have reasonably occurred as a consequence of oxygen therapy (usual or conservative)</td>
</tr>
<tr>
<td>• Sinus tachycardia</td>
<td>• Not events that are part of the natural primary disease process or expected complications of critical illness (e.g. multi-organ failure)</td>
</tr>
<tr>
<td>• Supraventricular tachycardia</td>
<td></td>
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<tr>
<td>• Atrial fibrillation</td>
<td></td>
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<tr>
<td>• Myocardial ischaemia/infarction</td>
<td></td>
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<tr>
<td>• Mesenteric ischaemia</td>
<td></td>
</tr>
</tbody>
</table>

*if readmitted to ICU within 90 days, safety monitoring recommences*
Thank you

- Any questions?

uk-rox@icnarc.org
020 7269 9277
icnarc.org/Our-Research/Studies/UK-ROX