









REVIEW ARTICLE

Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU)—Protocol for a randomised clinical trial comparing a lower vs a higher oxygenation target in adults with acute hypoxaemic respiratory failure

Olav L. Schjørring^{1,2,3}  | Anders Perner^{3,4}  | Jørn Wetterslev^{3,5}  | Theis Lange^{3,6,7}  |
 Frederik Keus⁸  | Jon H. Laake⁹  | Marjatta Okkonen¹⁰ | Martin Siegemund¹¹ |
 Matthew Morgan^{12,13}  | Katrin M. Thormar¹⁴ | Bodil S. Rasmussen^{1,2,3}  |
 and the HOT-ICU Investigators

¹Department of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Aalborg, Denmark

²Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

³Centre for Research in Intensive Care (CRIC), Copenhagen, Denmark

⁴Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁵Copenhagen Trial Unit, Department 7812, Centre for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁶Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark

⁷Center for Statistical Science, Peking University, Peking, China

⁸Department of Critical Care, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

⁹Division of Emergencies and Critical Care, Oslo University Hospital, Rikshospitalet, Oslo, Norway

¹⁰Department of Perioperative, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland

¹¹Department of Anaesthesia and Intensive Care, University Hospital Basel, Basel, Switzerland

¹²Critical Care Research, University Hospital of Wales, Cardiff, UK

¹³Cardiff University School of Medicine, Wales, UK

¹⁴Department of Anaesthesia and Intensive Care, University Hospital Reykjavik, Landspítali, Reykjavik, Iceland

Correspondence

Olav L. Schjørring, Department of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Denmark.
 Email: o.schjoerring@rn.dk

Funding information

The trial is funded by the Innovation Fund Denmark (4108-00011A) and supported by the Novo Nordisk Foundation, the Obel Family Foundation, Regionernes Medicinpulje, the Danish Society of Anaesthesia and Intensive Care Medicine and the ICU Symposium Hindsø. The funding sources will have no influence on the trial design, the scientific content of the protocol, the trial conduct, the DMSC, the data collection or data analysis, the interpretation of the results or the final publication.

Background: Acutely ill adults with hypoxaemic respiratory failure are at risk of life-threatening hypoxia, and thus oxygen is often administered liberally. Excessive oxygen use may, however, increase the number of serious adverse events, including death. Establishing the optimal oxygenation level is important as existing evidence is of low quality. We hypothesise that targeting an arterial partial pressure of oxygen (PaO₂) of 8 kPa is superior to targeting a PaO₂ of 12 kPa in adult intensive care unit (ICU) patients with acute hypoxaemic respiratory failure.

Methods: The Handling Oxygenation Targets in the ICU (HOT-ICU) trial is an outcome assessment blinded, multicentre, randomised, parallel-group trial targeting PaO₂ in acutely ill adults with hypoxaemic respiratory failure within 12 hours after ICU admission. Patients are randomised 1:1 to one of the two PaO₂ targets throughout ICU stay until a maximum of 90 days. The primary outcome is 90-day mortality. Secondary outcomes are serious adverse events in the ICU, days alive without organ support and days alive out of hospital in the 90-day period; mortality, health-related

quality-of-life at 1-year follow-up as well as 1-year cognitive and pulmonary function in a subgroup; and an overall health economic analysis. To detect or reject a 20% relative risk reduction, we aim to include 2928 patients. An interim analysis is planned after 90-day follow-up of 1464 patients.

Conclusion: The HOT-ICU trial will test the hypothesis that a lower oxygenation target reduces 90-day mortality compared with a higher oxygenation target in adult ICU patients with acute hypoxaemic respiratory failure.

1 | INTRODUCTION

Oxygen is essential to sustain human life and thus patients with acute hypoxaemic respiratory failure admitted to the intensive care unit (ICU) are all treated with supplemental inspired medical oxygen to avoid life-threatening hypoxia. In the ICU setting, oxygen therapy is guided by descriptive studies,^{1,2} four small randomised clinical trials (RCTs)³⁻⁶ and small before-and-after trials,^{7,8} all indicating harmful effects of excessive oxygen supplementation. A recent meta-analysis of trials in acutely ill patients overall⁹ underlined the potential detrimental effect of hyperoxaemia. Nevertheless, the tendency in ICUs is towards a liberal use of oxygen therapy¹⁰⁻²² and noteworthy, despite self-reported restrictive preferences among ICU nurses and physicians.²³⁻²⁶ Importantly, hypoxaemia is associated with increased mortality^{10,12,18,27} as it may lead to a low tissue oxygen tension (PO₂). The 'critical' tissue PO₂ however, defined as the value below which oxidative cellular metabolism fails, is not measurable in daily clinical practice, but it is as low as 0.13 kPa in isolated mitochondria.²⁸ Therefore, since only global oxygenation can be measured, liberal use of oxygen is likely to provide a too wide buffer of safety against life-threatening hypoxia. The potential harmful adverse effects of hyperoxaemia includes direct or indirect cellular damage mediated by reactive oxygen species,²⁹⁻³³ hyperoxaemic vasoconstriction^{34,35} with following paradoxical risk of tissue hypoxia, and formation of absorption atelectases.³⁶⁻³⁸ Targeting sub-normal oxygenation levels may, however, increase the risk of sudden desaturations due to the proximity to the steep slope of the oxygen dissociation curve.³⁹ This emphasises the importance of continuous pulse oximetry during restrictive oxygenation practices, and vigilance of the nursing staff to avoid or minimise episodes of definitive hypoxaemia. When such precautions are taken however, an oxygenation target of 8 kPa may be superior to the conventional liberal approach of oxygen supplementation observed in current clinical practice.¹⁰⁻²² Restrictive oxygenation is recommended in patients with chronic obstructive pulmonary disease (COPD) outside the ICUs targeting an arterial oxygen saturation measured by pulse oximetry (SpO₂) of 88% to 92%^{40,41}; in ICU patients with acute respiratory distress syndrome (ARDS) 'low normoxaemia' defined as an arterial partial pressure of oxygen (PaO₂) from 7.3 to 10.7 kPa is often targeted,^{42,43} however, not recommended in current clinical guidelines due to lack of evidence.^{44,45}

Editorial Comment

This is the protocol for the largest ongoing multinational randomised clinical trial on higher vs lower oxygenation targets in the ICU. It is set to be one of the most important ICU trials, guiding oxygenation targets for critically ill patients globally.

The optimal level of oxygenation in ICU patients remains unknown, especially when oxygenation levels are not definitively hyperoxaemic. Hence, trials in ICU patients comparing 'strict normoxaemia' defined as within the normal reference range of PaO₂ from approximately 10.7 to 13.3 kPa,⁴⁶ to 'low normoxaemia' are urgently needed.

A target PaO₂ of 8 kPa and a target PaO₂ of 12 kPa would both not a priori be considered beneficial or harmful. Therefore, whichever target performs best with respect to all-cause mortality, serious adverse events (SAEs), use of life support in the ICU and health-related quality-of-life has to be investigated in a large, pragmatic, randomised trial with the lowest possible risk of bias.

We hypothesise that targeting a PaO₂ of 8 kPa reduces 90-day mortality compared with targeting a PaO₂ of 12 kPa in adult patients with hypoxaemic respiratory failure who are acutely admitted to the ICU.

2 | METHODS

2.1 | Trial design

The Handling Oxygenation Targets in the ICU (HOT-ICU) trial is an investigator-initiated, pragmatic, international, multicentre, randomised, outcome-assessor blinded, parallel-group trial of a lower oxygenation target vs a higher oxygenation target in adult patients with acute hypoxaemic respiratory failure acutely admitted to the ICU. Patients are randomised 1:1 within 12 hours after ICU admission and stratified by site, known COPD, and active haematological malignancy.

The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.⁴⁷ The SPIRIT 2013 checklist is presented in Appendix

S1. A preliminary systematic review on the effect of lower vs higher oxygenation targets on mortality, including a trial sequential analysis was conducted⁴⁸ as recommended.^{49,50} The preliminary analysis revealed no evidence to support neither a high nor a low oxygenation target.

2.2 | Registration

The trial was prospectively registered at European clinical trials database (EudraCT number 2017-000632-34) and at ClinicalTrials.gov (Identifier: NCT03174002), registered June 2, 2017.

2.3 | Setting

Intensive care units in university and non-university hospitals in Denmark, Finland, the Netherlands, Norway, Switzerland, the United Kingdom and Iceland that admit adult patients. A complete list of including sites can be found at ClinicalTrials.gov (Identifier: NCT03174002).

2.4 | Inclusion criteria

Patients aged 18 years or older, acutely admitted to the ICU, having an arterial line for PaO₂ monitoring, and receiving supplemental oxygen with a flow of at least 10 litres per minute in an open system irrespective of any flow of atmospheric air, or a fraction of inspired oxygen (FiO₂) of at least 0.50 in a closed system including invasive or non-invasive ventilation or continuous positive airway pressure (CPAP) systems, and who are expected to receive supplemental oxygen for at least 24 hours in the ICU, will be evaluated for participation.

2.5 | Exclusion criteria

Patients will be excluded from the trial if they meet any of the following criteria: (a) cannot be randomised within 12 hours of ICU admission, (b) receives chronic mechanical ventilation for any reason, (c) home supplemental oxygen use, (d) previously treated with bleomycin, (e) solid organ transplant planned or conducted during current hospital admission, (f) withdrawal from active therapy or brain death is deemed imminent, (g) pregnancy, that is, fertile woman with positive human chorionic gonadotropin (hCG) or plasma-hCG, (h) carbon monoxide poisoning, (i) cyanide poisoning, (j) methaemoglobinaemia, (k) paraquat poisoning, (l) any condition expected to involve the use of hyperbaric oxygen therapy, (m) sickle cell disease, (n) consent not obtainable according to national regulations and (o) previously randomised into the HOT-ICU trial.

2.6 | Screening and randomisation

All patients fulfilling the inclusion criteria within 12 hours from ICU admission will be screened by local investigators using a

central web-based screening system. Patients are eligible if they fulfil all inclusion criteria and none of the exclusion criteria. Eligible patients will be randomised 1:1 via the screening system using a computer-generated allocation sequence list according to the stratification variables, and permuted blocks of varying sizes; all processes are concealed for patients, clinicians and trial investigators.

Inclusion and exclusion of patients will be reported as according to the Consolidated Standards of Reporting Trials (CONSORT) statement.⁵¹

2.7 | Interventions

Enrolled patients will be randomly allocated to a PaO₂ oxygenation target equal to 8 kPa (60 mm Hg) or a PaO₂ oxygenation target equal to 12 kPa (90 mm Hg) throughout the length of stay in the ICU, including any readmissions up until 90 days from randomisation. The oxygenation target will be achieved by titration of the FiO₂ from 0.21 to 1.00 in both intervention groups. Deviation above the allocated oxygenation target will be allowed only if FiO₂ = 0.21 and deviation below the allocated oxygenation target will be allowed only if FiO₂ = 1.00. Given the pragmatic design of the trial, choice of oxygen supplementation devices and ventilator settings other than the FiO₂ are at the discretion of the treating clinicians. Ventilator settings will be registered daily enabling assessment of any intervention group differences other than the FiO₂, in the subgroup of mechanically ventilated patients. In both intervention groups, additional oxygen supplementation during ICU procedures, as well as during transportation, surgery and radiological examinations will be at the discretion of the treating clinicians; however, it will be requested to maintain the assigned oxygenation target whenever possible. Pre-oxygenation with FiO₂ = 1.0 prior to or during endotracheal procedures should be avoided if possible, alternatively, pre-oxygenation for a maximum duration of 1 minute prior to endotracheal suction and for a maximum duration of 3 minutes prior to intubation is allowed.

2.8 | Withdrawal and discontinuation of trial intervention

Patients will be withdrawn from the trial intervention at any time if informed consent is retracted or not given as according to national regulations. Data registration from a withdrawn patient will continue, unless consent for this is also withdrawn. If a patient experiences a suspected unexpected serious adverse reaction (SUSAR) related to oxygen supplementation, the patient will be withdrawn from the trial immediately; data registration will, however, continue. In all withdrawn patients, trial intervention will be stopped and further oxygen supplementation in the ICU will be at the discretion of the treating clinicians. Patients withdrawn from the trial, were data can be acquired as according to national regulations, will be followed up and included in the intention-to-treat analyses as well as in the per-protocol analyses if the criteria for these are met.

Patients transferred to an ICU participating in the HOT-ICU trial will keep the allocated oxygenation target during ICU admission up until 90 days after randomisation. Patients transferred to an ICU not participating in HOT-ICU will be considered discharged from the ICU. All patients will be followed up for the primary outcome, and for as many of the secondary outcomes as possible through national registers, phone calls, and/or patient charts.

A patient can be discontinued from the intervention by the clinicians at any time if the patient experiences intolerable adverse events believed to be related to the trial intervention. In these cases, the oxygenation target should be reinstated if the trial intervention at a later point is considered safe by the treating clinicians. In either case, the patient remains in the trial and will be included in the intention-to-treat population, and per-protocol populations if the criteria are met.

Flawed randomisations, that is, patients found not to have fulfilled the inclusion criteria at randomisation, or who fulfilled one or more of the exclusion criteria at randomisation, will remain in the trial.

2.9 | Outcome measures

The primary outcome measure is all-cause mortality 90 days after randomisation. Secondary outcome measures include: (a) number of patients with one or more SAE in the ICU after randomisation defined as new episode of shock, new episodes of myocardial or intestinal ischaemia or ischaemic stroke; (b) days alive without the use of respiratory support, renal replacement therapy or circulatory support in the 90-day period; (c) days alive and out of hospital in the 90-day period; (d) mortality 1 year after randomisation; (e) health-related quality-of-life assessed by EuroQol 5 dimensions 5 level questionnaire and EQ visual analogue scale (EQ-5D-5L)⁵² 1 year after randomisation (patients who have died will be assigned the lowest possible EQ-5D-5L scores); (f) cognitive function 1 year after randomisation assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)⁵³ at selected sites; (g) a health economic analysis, the analytic details will be based on the result of the trial and specified later on (cost-effectiveness vs cost-minimisation analyses); and (h) pulmonary function 1 year after randomisation at selected sites as assessed using whole body plethysmography and diffusion capacity. This latter outcome has been planned post hoc.

The specific elements of the above composite outcomes will be reported in a supplement to the primary publication.

An overview of the enrolment, interventions and assessments procedures as according to the SPIRIT 2013 statement⁴⁷ is presented in Table 1.

2.10 | Blinding

The trial intervention is not blinded for investigators, clinicians or patients. The primary outcome of 90-day mortality will be drawn from electronic patient systems relying on central national registers

and will thus be assessed blinded. Similar procedure is applied for the secondary outcome of 1-year mortality. EQ-5D-5L and RBANS interviews, as well as pulmonary function tests will be conducted by research staff members who are not employed in the ICUs, without access to the eCRF or patient files and thus blinded to the trial interventions. Since local investigators will provide all other outcomes from the patients' medical files, blinding of outcome assessment is not feasible for these remaining outcomes. The trial statistician will be blinded for the allocation during all analyses. The members of the data monitoring and safety committee (DMSC) will remain blinded unless 1) they request otherwise or 2) the interim analysis has provided strong indications of one of the interventions being harmful. The writing committee will remain blinded for the allocation while drafting the abstract for the primary publication.

2.11 | Subgroups

We will compare the primary outcome measure in five predefined subgroups (a) patients with shock at randomisation (yes/no), (b) patients receiving invasive mechanical ventilation at randomisation (yes/no), (c) type of ICU admission (medical/elective surgical/emergency surgical), (d) patients with known COPD at randomisation (yes/no) and (e) patients with acute traumatic brain injury at randomisation (yes/no). Furthermore, the primary outcome measure will be compared in four subgroups that were not pre-specified: (a) patients with active haematological malignancy (yes/no), (b) patients resuscitated from cardiac arrest prior to randomisation (yes/no), (c) patients with ARDS at randomisation (yes/no) and (d) patients receiving oxygen supplementation through a closed system at randomisation according to baseline PaO₂/FiO₂ ratio (<13.3 kPa; ≥13.3 to < 26.7 kPa; ≥26.7 to < 40.0 kPa; and ≥40.0 kPa).

2.12 | Data registration and monitoring

All data will be entered into a central web-based, password protected, encrypted electronic case report form (eCRF) system supplied and supported by the Copenhagen Trial Unit using the clinical data management system OpenClinica® software (OpenClinica, LLC, Waltham, MA 02451, USA). Paper versions of the eCRF are used only during system malfunction. Details and definitions of the data collected are presented in Appendix S2.

Full external monitoring of registered data is applied at all trial sites following a monitoring plan developed in collaboration with the good clinical practice (GCP) unit at Aalborg and Aarhus University Hospitals according to GCP standards.⁵⁴ Central monitoring is done by Sponsor using the eCRF data only.

2.13 | Adverse and serious adverse events

Selected SAEs as defined under secondary outcome measures will be registered daily in the eCRF. When an ischaemic SAE is registered (new myocardial ischaemia, new intestinal ischaemia or new ischaemic stroke) clinicians will be asked for possible relation to the

TABLE 1 Overview of the schedule of enrolment, interventions and assessments as according to the SPIRIT 2013 statement

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation (Days from randomisation)			
	<i>ICU admission (+ 0-12 hours)</i>	<i>Time of randomisation (0)</i>	<i>0</i>	<i>ICU discharge /day 90</i>	<i>Follow-up</i>	
					<i>90</i>	<i>365</i>
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
<i>Oxygenation target 8 kPa</i>			↔			
<i>Oxygenation target 12 kPa</i>			↔			
ASSESSMENTS:						
<i>Baseline variables (general patient information, respiratory support, respiratory status, acute illness parameters, SOFA score and chronic comorbidities)</i>	X	X				
<i>Mortality</i>					X	X
<i>Serious adverse events in the ICU</i>			↔		X	
<i>Days alive without organ support</i>			↔		X	
<i>Days alive and out of hospital</i>			↔		X	
<i>EuroQol (EQ-5D-5L)</i>						X
<i>Neuropsychological function (RBANS)</i>						X*
<i>Pulmonary function</i>						X*

ICU: Intensive Care Unit; EQ-5D-5L: EuroQol 5 dimensions 5 level questionnaire and EQ visual analogue scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; SOFA: Sequential Organ Failure Assessment.

*At selected sites.

allocated oxygenation target. If a relation is suspected an automatic warning will be sent to the coordinating centre, hereby enabling the Sponsor to continuously evaluate trial safety and to decide whether it represents a serious adverse reaction or SUSAR and act accordingly. Any other SAEs according to the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use GCP (ICH-GCP) definition⁵⁴ will not be systematically recorded, but will be evaluated continuously by primary site investigators and co-investigators in their daily clinical practice.

The three adverse reactions to normobaric medical oxygen are atelectasis, pleuritis and ARDS⁵⁵; all common in critically ill patients admitted to the ICU with acute hypoxaemic respiratory failure. They are therefore indistinguishable from the adverse events caused by the underlying pulmonary pathophysiology. However, differences in the severity of atelectasis and of ARDS will be captured by daily registrations of FiO_2 and PaO_2 enabling the calculation of a $\text{PaO}_2/\text{FiO}_2$ ratio.

If a patient experiences a SUSAR, this will be reported to the relevant authorities as required by the national and European regulations.

All trial sites have insurances for participating patients either through the national health insurances or through specifically supplied local trial insurances as required according to the specific trial sites and national regulations.

2.14 | Approvals

The HOT-ICU trial is approved by the Danish Health and Medicine Agency (AAUH-ICU-01, approved 31 May 2017), the Committee on Health Research Ethics in the North Denmark Region (N-20170015, approved 22 May 2017), the Danish Data Protection Agency (2008-58-0028, approved 27 March 2017) and by all required authorities in participating countries. All patients will be enrolled after consent to participate has been obtained as according to national regulations.

2.15 | Statistics

The primary analysis will be conducted in the intention-to-treat population⁵⁶ being all randomised patients except those were follow-up cannot be conducted due to withdrawal of consent as according to national regulations.^{54,57,58} The primary outcome of 90-day mortality in the intervention groups will be compared using a generalised linear model with a log-link and binomial error distribution with adjustment for stratification variables (site, known COPD and active haematological malignancy).⁵⁹ Significance of the intervention will be assessed based on *P*-values from this regression analysis and risk ratios with 95% confidence intervals are readily available from it. The primary analysis will be supplemented with Kaplan-Meier plots (not accounting for stratification variables) and Cox proportional hazard models with adjustment for stratification variables.

A secondary analysis will be performed adjusting for the stratification variables and for major prognostic baseline differences: age,

active metastatic cancer, type of admission (medical, elective surgical or emergency surgical) and baseline Sequential Organ Failure Assessment (SOFA) score.⁶⁰

One pre-planned sensitivity analysis will be conducted in the per-protocol population defined as all patients except those with one or more major protocol violations (MPVs); that is, both the highest and the lowest registered PaO_2 in one 12-hour interval from 06:00 to 18:00 or from 18:00 to 06:00 are at least 1.0 kPa above the PaO_2 target if both FiO_2 s are above 0.21, OR at least 1.0 kPa below the PaO_2 target if both FiO_2 s are below 1.00.

Three post-trial-initiation planned sensitivity analyses will be conducted. The first analysis will be the new primary per-protocol population, which excludes patients with an MPV as defined by the pre-planned per-protocol population in two or more consecutive 12-hour intervals, corresponding to the patient being at least 24 hours off target; only consecutive MPVs that deviate to the same side (either above OR below the allocated oxygenation target) will exclude the patient. The second sensitivity analysis will establish the impact of higher vs lower oxygenation overall. It excludes patients allocated to 12 kPa with MPVs deviating below the oxygenation target in two or more consecutive 12-hour intervals AND it excludes patients allocated to 8 kPa with MPVs deviating above the oxygenation target in two or more consecutive 12-hour intervals. In this sensitivity analysis the patients with MPVs, which draws the oxygenation groups towards each other, will be removed. The third sensitivity analysis will evaluate the impact of too-high or too-low oxygenation. It excludes patients allocated to 12 kPa with MPVs deviating above the oxygenation target in two or more consecutive 12-hour intervals AND it excludes patients allocated to 8 kPa with MPVs deviating below the oxygenation target in two or more consecutive 12-hour intervals. In this sensitivity analysis the patients with MPVs, which draws the oxygenation groups away from each other, will be removed.

A two-sided *P* value of less than 0.05 will be considered statistically significant. *P*-values for the secondary outcomes will be adjusted for multiple testing. We will present the intervention effect expressed as relative risk with 95% CIs in the overall population as well as in the planned subpopulations.

A predefined detailed statistical analyses plan including models for all secondary outcomes will be provided in a separate publication submitted prior to inclusion of last patient, or in the case that the trial is prematurely terminated, submitted prior to closure of the trial database.

2.16 | Sample size calculations

To detect or reject a true 20% relative risk reduction, achieving a maximal type 1 error of 5% and type 2 error (power) of 90%, we will randomise 2928 patients. The sample size estimation was based on a control group 90-day mortality (target PaO_2 of 12 kPa) of 25%^{27,61} and allocation 1:1 to the two groups. We will be able to detect or refute an absolute risk reduction of 5% point or more, corresponding

to a number needed to treat of 20 or less. To maintain power in the statistical analysis, we will adjust the primary analyses for the stratification variables.

2.17 | Data monitoring and safety committee (DMSC)

An independent DMSC will oversee the trial during the trial period following the predefined Charter for the DMSC (Appendix S3).

A planned interim analysis will be conducted when the first 1464 patients (50% of the sample size) have completed 90-day follow-up. The DMSC may request unplanned interim analyses at any time.

The DMSC may recommend pausing or stopping the trial if group-difference in the primary outcome measure or in SAEs are found in any interim analysis with statistical boundaries based on O'Brien-Fleming alpha-spending function.⁶² If an analysis of the interim data from the 1464 patients fulfils the Lan-DeMets stopping criterion⁶², the inclusion of further patients will be paused and an analysis including all randomised patients will be performed. If this second analysis also fulfils the Lan-DeMets' stopping criterion according to the group sequential monitoring boundaries, the Management Committee may stop the trial.⁵⁴ Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping the trial due to expected futility of showing a 20% relative risk ratio reduction will not be an option as intervention effect <20% relative risk ratio reduction of all-cause mortality may be clinically relevant.

2.18 | Availability of data and material

The clean electronic trial database file will be delivered to the EudraCT Database and to the Danish Data Archive. All trial documents, including protocol amendments will be available on the public HOT-ICU trial website (www.cric.nu/hot-icu) and communicated to relevant parties through monthly newsletters. The trial results will be sought published in a relevant peer reviewed scientific journal and linked to the trial website.

3 | DISCUSSION

Oxygen is a medicine that has been used for decades with a continuing tendency towards liberal use. This is highlighted in recently published observational studies in critically ill patients admitted to ICUs in Europe,^{19,27} in New Zealand and Australia¹² and in the US,¹⁸ all showing U-shaped associations between arterial oxygenation and mortality. Noteworthy, the PaO₂ associated with the lowest mortality was highly variable in these studies—from 10 kPa²⁷ to as high as 40 kPa.¹⁸ Taking the observational study design into consideration however, causality cannot be assumed, and the associations found may merely represent differences in disease severity or be reflections of the preferred oxygenation levels

in the included ICUs. Therefore, the optimal target interval resulting in the lowest mortality risk remains uncertain. Several RCTs on liberal vs conservative oxygen therapy in heterogeneous groups of acutely ill patients and in various clinical settings have been conducted. These trials were recently grouped in a systematic review and meta-analysis,⁹ which concluded that there is high-quality evidence showing that liberal oxygen therapy increases mortality without improving other patient-important outcomes. However, the oxygenation targets of the included trials were highly variable, as were the intended durations of the interventions, ranging from 1 to 144 hours. Importantly, trials in patients with and without respiratory failure were included in the analysis. Only three of the included trials were conducted in ICU patients,⁴⁻⁶ of which the trial with the highest weight (32%),⁵ was stopped prematurely after an unplanned interim analysis. Based on supplementary analysis, the authors of the systematic review⁹ concluded that treatment with oxygen could become unfavourable in acutely ill patients if resulting in an SpO₂ above 94%-96%. However, this specific upper target of SpO₂ is not supported by the trials with the highest weight in the mortality analysis,^{5,63-65} as these studies effectively all investigated normoxaemia vs hyperoxaemia with SpO₂ above 94%-96% in the conservative oxygenation groups. Nevertheless, this upper SpO₂ target has recently been implemented in a clinical guideline on oxygen therapy.⁶⁶ Despite this guideline being published, several questions remain unanswered. Most importantly, how will oxygenation targets of strict normoxaemia vs low normoxaemia affect short- and long-term patient-important outcomes⁶⁷ in patients admitted to the ICU, and in those with hypoxaemic respiratory failure? The HOT-ICU trial aims to answer these important questions.

The trial will include patients with hypoxaemic respiratory failure only, and the level of oxygen supplementation defines the patients as being hypoxaemic in the pragmatic trial design. The reason for not using PaO₂ as part of the inclusion criterion is based on the assumption that physicians will not give supplementary oxygen over the designated threshold in patients without hypoxaemic respiratory failure. As the threshold of oxygen supplementation is high, we expect that all patients included will have hypoxaemic respiratory failure with a PaO₂/FiO₂ ratio below 40 kPa.

The oxygenation targets in the HOT-ICU trial are defined by PaO₂ levels. The choice of PaO₂ over arterial oxygen saturation (SaO₂) or SpO₂ as target parameter is based on the fact that the level of hyperoxaemia is uncontrollable if using only the SaO₂ or SpO₂ due to the sigmoid shape of the oxygen dissociation curve.^{39,68} Therefore, if SaO₂ or SpO₂ above 95% defines the oxygenation target, uncontrollable levels of hyperoxaemia will occur as underlined in a recent observational study.⁶⁹ Additionally, ICU doctors in Northern Europe prefer using PaO₂ over SaO₂ as the target parameter for oxygenation.²⁶

The choice of protocolling a fixed normoxaemic oxygenation target in the control group rather than standard care at clinicians' discretion is based on the large variation in oxygenation levels observed in ICU cohorts worldwide with median and

mean PaO₂ levels ranging from 9.8 to 23.0 kPa.^{10-12,14-16,18} As the HOT-ICU trial is international, a highly variable approach to oxygen supplementation can be assumed, thus a non-protocolled standard care in the control group would induce a risk of masking any deductions about the actual oxygenation strategy used. Furthermore, a pilot trial⁴ which confirmed equipoise of the intervention groups in the HOT-ICU trial, used a protocolled oxygenation target in the liberal oxygenation control group, a target that corresponds to the higher oxygenation target of 12 kPa in the HOT-ICU trial.

The choice of mortality as primary outcome is based on the high mortality rates in ICU patients⁷⁰ and in mechanically ventilated patients in particular,⁷¹ and on the probability of detecting a difference in mortality by interventions in the ICU, especially for life-support interventions. Only mortality as the primary outcome will weigh the totality of the potential positive and negative effects of a higher vs a lower oxygenation strategy. Finally, the recent systematic review,⁹ which suggested reduced all-cause mortality with conservative oxygen therapies in acutely ill patients overall, further justifies the choice of mortality as the primary outcome.

4 | PERSPECTIVE

The design of the HOT-ICU trial aims to minimise the risk of systematic errors and the trial will provide valuable information on benefits and/or harmful effects of an oxygenation target of either 8 kPa or an oxygenation target of 12 kPa in patients acutely admitted to the ICU with need of oxygen supplementation due to hypoxaemic respiratory failure, including both short-term and long-term outcomes. Being the largest trial on the subject, the trial will add considerably to the cumulated evidence and to the overall knowledge of optimal oxygenation targets in the ICU, with the potential to reduce both mortality and morbidity as well as costs in the ICU. The HOT-ICU trial will assist in guiding future clinical practice, ensuring a more evidence-based use of medical oxygen in the ICU.

5 | TRIAL STATUS

The trial is currently recruiting at 28 active sites. The first patient was randomised on the 20th of June 2017. At present (22 January 2019), 1291 patients have been included. The current protocol version is version 2.0 of 12 December 2018. The last patient is expected to be included ultimo 2019.

ACKNOWLEDGEMENTS

We thank the participating patients and relatives, site investigators and the clinical staff at all trial sites, the DMSC members (professor Jean-François Timsit, Bichat Teaching Hospital, Paris Diderot University, Paris, France; professor Daniel De Backer, the Free

University Hospital, Brussels, Belgium; and assistant professor Andreas Kryger Jensen, Section of Biostatistics, Department of Public Health, University of Copenhagen, Denmark), our funding sources and Centre for Research in Intensive Care (CRIC).

CONFLICT OF INTEREST

The Department of Intensive Care, Rigshospitalet has received funds for research from Fresenius Kabi, CSL Behring and Ferring Pharmaceuticals.

AUTHORS' CONTRIBUTIONS

OLS and BSR drafted the protocol and the manuscript for this paper in close collaboration with AP, JW and TL. FK, JHL, MO, MS, MM and KMT all made substantial contributions to the process of developing the protocol and contributed with scientific input for the protocol and for this manuscript. All authors have read and approved the final manuscript. All authors are members of the HOT-ICU Steering Committee with BSR as sponsor and principal investigator of the HOT-ICU trial, OLS as coordinating investigator and FK, JHL, MO, MS, MM, KMT and OLS as national principal investigators. The HOT-ICU Management Committee consists of BSR, OLS, AP, JW and TL. The Management Committee will draft the final article.

ORCID

Olav L. Schjørring  <https://orcid.org/0000-0002-7749-6003>

Anders Perner  <https://orcid.org/0000-0002-4668-0123>

Jørn Wetterslev  <https://orcid.org/0000-0001-7778-1771>

Theis Lange  <https://orcid.org/0000-0001-6807-8347>

Frederik Keus  <https://orcid.org/0000-0003-1516-1475>

Jon H. Laake  <https://orcid.org/0000-0001-6157-5359>

Matthew Morgan  <https://orcid.org/0000-0002-2357-7190>

Bodil S. Rasmussen  <https://orcid.org/0000-0003-2190-145X>

REFERENCES

1. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2014;18:711.
2. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of cohort studies. *Crit Care Med*. 2015;43:1508-1519.
3. Gomersall CD, Joynt GM, Freebairn RC, Lai CK, Oh TE. Oxygen therapy for hypercapnic patients with chronic obstructive pulmonary disease and acute respiratory failure: a randomized, controlled pilot study. *Crit Care Med*. 2002;30:113-116.
4. Panwar R, Hardie M, Bellomo 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;193:43-51.

5. Girardis M, Busani S, Damiani E, 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):1583-1589.
6. Asfar P, Schortgen F, Boissrame-Helms J, et al. Hyperoxia and hyper-tonic saline in patients with septic shock (HYPER2S2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med*. 2017;5(3):180-190.
7. Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative oxygen therapy in mechanically ventilated patients: a pilot before-and-after trial. *Crit Care Med*. 2014;42:1414-1422.
8. Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in critically ill patients: a before and after trial. *Crit Care Med*. 2016;44:554-563.
9. Chu DK, Kim LH-Y, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391:1693-1705.
10. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care*. 2008;12:R156.
11. de Graaff AE, Dongelmans DA, Binnekade JM, de Jonge E. Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of FiO₂. *Intensive Care Med*. 2011;37:46-51.
12. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med*. 2012;38:91-98.
13. Rachmale S, Li G, Wilson G, Malinchoc M, Gajic O. Practice of excessive F(I/O₂) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. *Respir Care*. 2012;57:1887-1893.
14. Panwar R, Capellier G, Schmutz N, et al. Current oxygenation practice in ventilated patients-an observational cohort study. *Anaesth Intensive Care*. 2013;41:505-514.
15. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. *J Crit Care*. 2013;28:647-654.
16. Itagaki T, Nakano Y, Okuda N, et al. Hyperoxemia in mechanically ventilated, critically ill subjects: incidence and related factors. *Respir Care*. 2015;60:335-340.
17. Young PJ, Beasley RW, Capellier G, et al. Oxygenation targets, monitoring in the critically ill: a point prevalence study of clinical practice in Australia and New Zealand. *Crit Care Resusc*. 2015;17:202-207.
18. Zhang Z, Ji X. Quadratic function between arterial partial oxygen pressure and mortality risk in sepsis patients: an interaction with simplified acute physiology score. *Sci Rep*. 2016;6:35133.
19. Helmerhorst HJ, Arts DL, Schultz MJ, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med*. 2017;45:187-195.
20. Dennis D, Torre L, Baker S, Hebden-Todd T. A snapshot of the oxygenation of mechanically ventilated patients in one Australian intensive care unit. *Anaesth Intensive Care*. 2017;45:359-364.
21. Egi M, Kataoka J, Ito T, et al. Oxygen management in mechanically ventilated patients: a multicenter prospective observational study. *J Crit Care*. 2018;46:1-5.
22. Kraft F, Andel H, Gamper J, Markstaller K, Ullrich R, Klein KU. Incidence of hyperoxia and related in-hospital mortality in critically ill patients: a retrospective data analysis. *Acta Anaesthesiol Scand*. 2018;62:347-356.
23. Mao C, Wong DT, Slutsky AS, Kavanagh BP. A quantitative assessment of how Canadian intensivists believe they utilize oxygen in the intensive care unit. *Crit Care Med*. 1999;27:2806-2811.
24. Eastwood GM, Reade MC, Peck L, Jones D, Bellomo R. Intensivists' opinion and self-reported practice of oxygen therapy. *Anaesth Intensive Care*. 2011;39:122-126.
25. Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. *Ann Intensive Care*. 2014;4:23.
26. Schjørring OL, Toft-Petersen AP, Kusk KH, et al. Intensive care doctors' preferences for arterial oxygen tension levels in mechanically ventilated patients. *Acta Anaesthesiol Scand*. 2018;62:1443-1451.
27. Dahl RM, Gronlykke L, Haase N, et al. Variability in targeted arterial oxygenation levels in patients with severe sepsis or septic shock. *Acta Anaesthesiol Scand*. 2015;59:859-869.
28. Sjöberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. *J Intern Med*. 2013;274:505-528.
29. Chow CW, Herrera Abreu MT, Suzuki T, Downey GP. Oxidative stress and acute lung injury. *Am J Respir Cell Mol Biol*. 2003;29:427-431.
30. Turrens JF. Mitochondrial formation of reactive oxygen species. *J Physiol*. 2003;552:335-344.
31. Zaher TE, Miller EJ, Morrow DM, Javdan M, Mantell LL. Hyperoxia-induced signal transduction pathways in pulmonary epithelial cells. *Free Radic Biol Med*. 2007;42:897-908.
32. Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care*. 2013;58:123-141.
33. Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to bedside review: the effects of hyperoxia during critical illness. *Crit Care*. 2015;19:284.
34. Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. *J Appl Physiol*. 1985;2003(95):2453-2461.
35. Bak Z, Sjöberg F, Rousseau A, Steinvall I, Janerot-Sjöberg B. Human cardiovascular dose-response to supplemental oxygen. *Acta Physiol (Oxf)*. 2007;191:15-24.
36. Rothen HU, Sporre B, Engberg G, Wegenius G, Hogman M, Hedenstierna G. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. *Anesthesiology*. 1995;82:832-842.
37. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Prevention of atelectasis during general anaesthesia. *Lancet*. 1995;345:1387-1391.
38. Aboab J, Jonson B, Kouatchet A, Taille S, Niklason L, Brochard L. Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome. *Intensive Care Med*. 2006;32:1979-1986.
39. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. *Breathe (Sheff)*. 2015;11:194-201.
40. Beasley R, Chien J, Douglas J, et al. Thoracic Society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'Swimming between the flags'. *Respirology*. 2015;20:1182-1191.
41. O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group, BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax*. 2017;72:ii1-ii90.
42. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. the Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301-1308.
43. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351:327-336.
44. Claesson J, Freundlich M, Gunnarsson I, et al. Scandinavian clinical practice guideline on mechanical ventilation in adults with

- the acute respiratory distress syndrome. *Acta Anaesthesiol Scand*. 2015;59:286-297.
45. Fan E, Del Sorbo L, Goligher EC, et al. An official American thoracic society/European society of intensive care medicine/Society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195:1253-1263.
 46. Kratz A, Ferraro M, Sluss PM, Lewandowski KB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *N Engl J Med*. 2004;351:1548-1563.
 47. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158:200-207.
 48. Barbateskovic M, Schjørring OL, Jakobsen JC, et al. Higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation for adult intensive care patients (Protocol). *Cochrane Database Syst Rev*. 2017.
 49. Young C, Horton R. Putting clinical trials into context. *Lancet*. 2005;366:107-108.
 50. World Health Organization. Research for Health. A Position Paper on WHO's Role and Responsibilities in Health Research. 2006; ACHR45/05.16 Rev.1.
 51. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8:18.
 52. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727-1736.
 53. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998;20:310-319.
 54. International conference on harmonisation; guidance on statistical principles for clinical trials; availability-FDA. Notice. *Fed Regist*. 1998;63:49583-49598.
 55. Air Liquide Healthcare. Summary of product characteristics - Medical oxygen. 2017; PL:15929/0005.
 56. DeMets DL, Cook T. Challenges of non-intention-to-treat analyses. *JAMA*. 2019;321(2):145.
 57. Gabriel SE, Normand SL. Getting the methods right—the foundation of patient-centered outcomes research. *N Engl J Med*. 2012;367:787-790.
 58. Schmiemann G. The preliminary draft of the methodology report by the Patient-Centered Outcomes Research Institute. *Z Evid Fortbild Qual Gesundheitswes*. 2012;106:496-499.
 59. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *BMJ*. 2012;345:e5840.
 60. Vincent J-I, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707-710.
 61. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41:833-845.
 62. Lan K, DeMets D. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.
 63. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033-2037.
 64. Roffe C, Nevatte T, Sim J, et al. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the stroke oxygen study randomized clinical trial. *JAMA*. 2017;318:1125-1135.
 65. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med*. 2018;378(2):200-202.
 66. Siemieniuk R, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ*. 2018;363:k4169.
 67. Mikkelsen ME, Anderson B, Christie JD, Hopkins RO, Lanken PN. Can we optimize long-term outcomes in acute respiratory distress syndrome by targeting normoxemia? *Ann Am Thorac Soc*. 2014;11:613-618.
 68. Schjørring OL, Rasmussen BS. The paramount parameter: arterial oxygen tension versus arterial oxygen saturation as target in trials on oxygenation in intensive care. *Crit Care*. 2018;22:324.
 69. Durlinger E, Spoelstra-de Man A, Smit B, et al. Hyperoxia: At what level of SpO₂ is a patient safe? A study in mechanically ventilated ICU patients. *J Crit Care*. 2017;39:199-204.
 70. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet*. 2010;376:1339-1346.
 71. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med*. 2010;38:1947-1953.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Schjørring OL, Perner A, Wetterslev J, et al. Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU)—Protocol for a randomised clinical trial comparing a lower vs a higher oxygenation target in adults with acute hypoxaemic respiratory failure. *Acta Anaesthesiol Scand*. 2019;63:956-965. <https://doi.org/10.1111/aas.13356>