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Published in:
Acta Anaesthesiologica Scandinavica

DOI (link to publication from Publisher):
10.1111/aas.14220

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Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Nielsen, F. M., Klitgaard, T. L., Bruun, N. H., Møller, M. H., Schjørring, O. L., & Rasmussen, B. S. (2023). Lower or higher oxygenation targets for acute Hypoxaemic respiratory failure: Protocol for an individual patient data meta-analysis. *Acta Anaesthesiologica Scandinavica*, *67*(6), 811-819. https://doi.org/10.1111/aas.14220

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Check for updates

Received: 24 January 2023 | Accepted: 29 January 2023

DOI: 10.1111/aas.14220

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Lower or higher oxygenation targets for acute Hypoxaemic respiratory failure: Protocol for an individual patient data meta-analysis

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Funding information
the Innovation Fund Denmark, Grant/Award Number: 4108-00011A; the Novo Nordisk Foundation; the Obel Family Foundation; Regionernes Medicinpulje; the Danish Society of Anaesthesiology and Intensive Care Medicine; the Intensive Symposium Hindsgavl; Danish Ministry of Higher Education and Research, Grant/Award Number: 0238-00004B

Abstract

Background: Supplemental oxygen therapy is central to the treatment of acute hypoxaemic respiratory failure, a condition which remains a major driver for morbidity and mortality in intensive care. Despite several large randomised clinical trials comparing a higher versus a lower oxygenation target for these patients, significant differences in study design impede analysis of aggregate data and final clinical recommendations.

Methods: This paper presents the protocol for conducting an individual patient data meta-analysis where full individual patient data according to the intention-to-treat principle will be pooled from the HOT-ICU and HOT-COVID trials in a one-step procedure. The two trials are near-identical in design. We plan to use a hierarchical general linear mixed model that accounts for data clustering at a trial and site level. The primary outcome will be 90-day all-cause mortality while the secondary outcome will be days alive without life-support at 90 days. Further, we outline 14 clinically relevant predefined subgroups which we will analyse for heterogeneity in the intervention effects and interactions, and we present a plan for assessing the credibility of the subgroup analyses.

Conclusion: The presented individual patient data meta-analysis will synthesise individual level patient data from two of the largest randomised clinical trials on targeted oxygen therapy in intensive care. The results will provide a re-analysis of the intervention effects on the pooled intention-to-treat populations and facilitate subgroup analyses with an increased power to detect clinically important effect modifications.

KEYWORDS
individual patient data meta-analysis, intensive care, supplemental oxygen therapy

Editorial Comment

How should oxygen be targeted for patients with hypoxemic respiratory failure admitted to an intensive care unit? This study protocol outlines the methods for an individual patient data meta-analysis based on the HOT-ICU and HOT-COVID trials.

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1 | BACKGROUND

Supplemental oxygen therapy is central for treating patients admitted to an intensive care unit (ICU) with acute hypoxaemic respiratory failure. Despite its widespread use, controversy exists on the optimal dosage.[1–4]

The handling oxygenation targets in the intensive care unit (HOT-ICU) trial was a large, randomised clinical trial (RCT) that investigated the harms and benefits of a lower versus a higher oxygenation target in adult ICU patients with acute hypoxaemic respiratory failure.[5] The trial compared an oxygenation strategy targeting a partial pressure of arterial oxygen (PaO_2) of 8 kPa to a PaO_2 target of 12 kPa. A total of 2928 patients were randomised, and no significant difference in the primary outcome, 90-day all-cause mortality, was observed.[5] Currently, the handling oxygenation targets in COVID-19 (HOT-COVID) trial is recruiting as an amendment to the HOT-ICU trial. It investigates the harms and benefits of a lower versus a higher oxygenation target in hypoxaemic ICU patients with proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia.[6] The HOT-COVID trial plans to randomise 780 patients with the primary outcome being the absolute number of days alive without life-support within 90 days from randomisation.

The uniformity of the two trials combined with access to complete datasets provides the possibility to conduct an individual patient data meta-analysis with minimal heterogeneity. Pooling of data allows for comparing and validating the primary outcomes of the HOT-ICU and HOT-COVID trials. Further, the analysis will facilitate robust interaction analyses of the intervention's effects in clinically important subgroups. Accordingly, we here present the protocol for an individual patient data meta-analysis based on complete datasets from the HOT-ICU trial and the HOT-COVID trial. The aim is to characterise benefits and harms for a lower versus a higher oxygenation target in patients acutely admitted to the ICU with hypoxaemic respiratory failure, and in clinically important subgroups.

2 | METHODS

The current protocol has been prepared in accordance with the preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P) statement,[7] see Appendix 1 for PRISMA-P checklist. Results will be reported as according to the preferred reporting items for a systematic review and meta-analysis of individual participant data (PRISMA-IPD) statement.[8] This protocol was prepared and submitted for publication prior to completion of the HOT-COVID trial, and prior to initiation of the individual patient data meta-analysis.

2.1 | Study design

The HOT-ICU and HOT-COVID trials were both investigator-initiated, pragmatic, international, randomised, parallel-group clinical trials. The HOT-ICU trial was conducted from 20 June 2017 to 3 August 2020, and randomised 2928 patients. The HOT-COVID trial randomised its first patient on 25 August 2020, and is currently recruiting; on 24 January 2023, 723 of the planned 780 patients had been enrolled. The protocol, statistical analysis plan, and results of the HOT-ICU trial have been published, while the protocol and statistical analysis plan for the HOT-COVID trial have been published.[5,6,9,10]

We will conduct an individual patient data meta-analysis of the HOT-ICU and HOT-COVID trials. All analyses will be conducted in accordance with the present protocol. Any deviations from the methods described below will be explicitly noted in the final publication of the analysis.

2.2 | Approvals

The HOT-ICU trial was approved by the Danish Health and Medicine Agency (AAUH-ICU-01, approved May 2017) with the HOT-COVID trial approved as an amendment. Both trials were approved by the Health Research Ethics Committee 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 the participating countries.

Both trials were registered on ClinicalTrials.gov (NCT03174002 and NCT04425031).

2.3 | Setting

Both trials are conducted in the intensive care setting. The HOT-ICU trial was conducted across 35 ICUs in seven countries while the HOT-COVID trial was conducted across 13 ICUs in five countries. Both university and non-university hospitals participated.

2.4 | Population

The investigated population is characterised by the criteria below.

2.4.1 | Inclusion criteria in the HOT-ICU and HOT-COVID trials

1. Acutely admitted to the ICU
2. Aged 18 years or older
3. Receiving supplemental oxygen with requirements of:

a. Open systems: a flow of at least 10 L per min
b. Closed systems:

i. HOT-ICU: a fraction of inspired oxygen (FiO_2) of at least 0.50 in a closed system, including invasive mechanical ventilation (IMV),

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non-invasive ventilation (NIV), or continuous positive airway pressure (CPAP)

ii. HOT-COVID: any FiO_2

4. Expected to receive supplemental oxygen for at least 24 h in the ICU
5. Having an arterial line for PaO_2 monitoring
6. HOT-COVID: any sample from airway secretions or nasopharyngeal swab positive for SARS-CoV-2 infection at any time leading to or during current hospital admission

2.4.2 | Exclusion criteria in HOT-ICU and HOT-COVID

1. Cannot be randomised within 12 h of ICU admission
2. Chronic mechanical ventilation for any reason
3. Home supplemental oxygen use
4. Previously treated with bleomycin
5. Solid organ transplant conducted during current hospital admission
6. Withdrawal from active therapy or brain death is imminent
7. Pregnancy, defined as fertile women with a positive human chorionic gonadotropin (hCG) test or positive plasma-hCG
8. Carbon-monoxide poisoning
9. Cyanide poisoning
10. Methaemoglobinaemia
11. Paraquat poisoning
12. Any condition expected to involve the use of hyperbaric oxygen therapy
13. Sickle cell disease
14. Consent not obtainable according to national regulations
15. Previously randomised into the HOT-ICU or the HOT-COVID trial

2.5 | Intervention and comparison

In both trials, patients were randomised 1:1 to receive targeted supplemental oxygen therapy with either a lower PaO_2 target of 8 kPa or a higher PaO_2 target of 12 kPa. The lower PaO_2 target is defined as the intervention, whereas the higher PaO_2 target is the defined as the control. Both trials are superiority trials.

2.6 | Outcomes

The primary outcome for this individual patient data meta-analysis is 90-day all-cause mortality. The secondary outcome is the absolute number of days alive without life-support within 90 days. Life-support is defined as either the use of any renal replacement therapy, vasopressor or inotropic support, or respiratory support defined as NIV, non-intermittent CPAP, or IMV. Further, we will perform sensitivity analyses of both the primary and secondary outcome with adjustment for clinically important baseline variables, being age as a continuous variable, presence or absence of metastatic cancer, admission type, and sequential organ failure assessment (SOFA) score as a count variable (Table 2).

2.7 | Subgroups analysed for interaction with both the primary and secondary outcome

We will assess if the intervention effect on both the primary and secondary outcome is influenced by categorical subgroups based on baseline patient characteristics. The baseline subgroups investigated for statistical interaction are age, sex, type of admission, ventilatory support, chronic obstructive pulmonary disease (COPD), pneumonia, intracranial pathology, heart disease, intestinal ischaemia, malignancy, shock, SARS-CoV-2 infection, and PaO_2:FiO_2 ratio among patients with respiratory support. The credibility of the investigated effect modification in each subgroup will be assessed using the 'Instrument to assess the Credibility of Effect Modification Analyses' (ICEMAN) tool.[11] A detailed overview of the subgroups and the expected direction of the intervention effect is presented in Table 1.

2.8 | Baseline description

Baseline characteristics will be reported for the combined HOT-ICU and HOT-COVID population and for each trial separately. Categorial variables will be reported as numbers and percentages, while continuous variables will be reported as medians with interquartile ranges. An overview of all baseline variables is presented in Table 2.

2.9 | Power estimation

Based on a control group mortality measured as 42.4% in the HOT-ICU trial and estimated at 40.0% in the HOT-COVID trial taking trial size into account, a control group mortality of 42.1% is expected. With a statistical power of 80% and a two-sided p value of .05 this study will be able to detect an absolute difference in mortality of 4.6%-points or more.

2.10 | General analytical principle

All analyses will be based on the intention-to-treat principle. The intention-to-treat population includes all randomised patients except those where follow-up could not be obtained due to withdrawal of consent according to national regulations.[14]

All tests for statistical significance will be two-sided. The alpha level will be .05 for the primary and the secondary outcome with 95% confidence intervals (CIs) with the same approach applied to the sensitivity analyses. The intervention effects in the subgroup analyses will

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TABLE 1 Overview of subgroups planned for analysis for interaction with the intervention.

Subgroups based on baseline registrations:	Specification:	Expected direction of intervention effect[a]
Age	Patients are categorised into two subgroups according to the population median age. Age ≥ median age Age < median age	We hypothesise a differential effect for patients in the two intervention groups according to age.
Sex	Categorial. Genotypic male or female	We hypothesise a differential effect for patients in the two intervention groups according to gender.
Admission type	Categorised into three subgroups: Medical Elective Surgical Emergency Surgical	We hypothesise a successively greater effect favouring the 8 kPa PaO_2 target for patients in elective surgical, medical, and emergency surgical admissions.
Ventilatory support	Categorised into three subgroups: IMV NIV or CPAP Open systems	We hypothesise a successively greater effect favouring the 8 kPa PaO_2 target for patients in open systems, NIV or CPAP, and IMV group.
COPD[b]	Categorical (Yes/No). Yes, if the patient at baseline were registered as having COPD	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with COPD.
Pneumonia	Categorical (Yes/No). Yes, if the patient at baseline were registered as having pneumonia	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with pneumonia.
Intracranial pathology	Categorical (Yes/No). Yes, if the patient at baseline were registered with either: Cardiac arrest Traumatic brain injury Haemorrhagic or ischaemic stroke	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with intracranial pathology.
Heart disease	Categorical (Yes/No). Yes, if the patient at baseline were registered with either: Ischaemic heart disease Chronic heart failure Acute myocardial infarction	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with heart disease.
Chronic dialysis	Categorical (Yes/No). Yes, if the patient at baseline were registered as receiving chronic dialysis	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with chronic dialysis.
Intestinal ischaemia	Categorical (Yes/No). Yes, if the patient at baseline were registered with intestinal ischaemia	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with intestinal is ischaemia.
Malignancy	Categorical (Yes/No). Yes, if the patient at baseline were registered with either: Active haematological malignancy[a] Metastatic cancer	We hypothesise an increased effect favouring the 8 kPa PaO_2 target in patients with malignancy.
Shock	Categorical (Yes/No). Yes, if the patient at baseline had both: Plasma lactate >2 mmol/L Use of continuous vasopressor or inotropes	We hypothesise an effect favouring the 12 kPa PaO_2 target for patients with shock.[3,5,6,12]
SARS-CoV-2 infection[c]	Categorical (Yes/No). Yes, for all patients in HOT-COVID, in HOT-ICU, yes, if patients tested positive for SARS-CoV-2 by any test at randomisation or during ICU admission	We hypothesise a differential effect for patients in the two intervention groups according to gender.
PaO_2:FiO_2 ratio	PaO_2:FiO_2 ratio is categorised into three subgroups. Only patients on IMV, NIV or CPAP at baseline are included in this subgroup. PaO_2:FiO_2 ratio > 26.6 mmHg 13.3 mmHg < PaO_2:FiO_2 ratio ≤ 26.6 mmHg PaO_2:FiO_2 ratio ≤ 13.3 mmHg	We hypothesise a successively greater effect favouring the 8 kPa PaO_2 target for patients in elective surgical, medical, and emergency surgical admissions.

Abbreviations: CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; HOT-ICU, handling oxygenation targets in the ICU, HOT-COVID, handling oxygenation targets in COVID-19; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; PaO_2, arterial partial pressure of oxygen; SaO_2, arterial oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]The expected direction of the intervention effect for each subgroup is consistent with those postulated in the HOT-ICU statistical analysis plan where nothing else is stated.[10]

[b]Stratification variable in the HOT-ICU trial.

[c]Patients diagnosed with SARS-CoV-2 during their ICU stay, but after randomisation, were included as having COVID-19 at baseline in the HOT-ICU trial since test availability and turnaround time were limited at the beginning of the pandemic leading to diagnostic delays.

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TABLE 2 Overview of baseline variables for both the HOT-ICU and HOT-COVID trial.

Table 2 Baseline characteristics	
Parameter	**Definition**
Age[a]	Calculated from birth to time of randomisation in years
Sex—no (%)	Genotypic
Median interval between hospital admission and randomisation (IQR)	Time from hospital admission to trial randomisation measured in days
Median interval between ICU admission and randomisation (IQR)	Time from ICU admission to trial randomisation measured in hours
Confirmed SARS-CoV-2 infection	HOT-ICU: Patients were registered if SARS-CoV-2 infection was confirmed by any test method at randomisation or during ICU admission HOT-COVD: Confirmed SARS-CoV-2 infection at randomisation was an inclusion criterion
Type of ICU admission—no (%)[a]	
Medical	Patients admitted to the ICU from a non-surgical setting
Elective surgical	Patients admitted directly from the operating or recovery room after elective surgery
Emergency surgical	Patients admitted directly from the operating or recovery room after emergency surgery
Acute illness[e]—no (%)	
Pneumonia	Defined by clinicians and noted in the patient files
Multiple trauma	Acute accident with lesions in two anatomical sites or more
Haemorrhagic or ischaemic stroke	Onset of symptoms prior to randomisation and verified by CT or MRI scan or diagnosed by a neurologist
Traumatic brain injury	Verified by fresh lesions on a CT or MRI scan
Myocardial infarction	Verified by ECG changes, significant rise in coronary biomarkers and/or acute PCI or CABG conducted
Intestinal ischaemia	Verified by surgery, gastroscopy, colonoscopy, or CT or MRI angiography
Cardiac arrest	Clinically diagnosed along with initiated cardiopulmonary resuscitation, leading to or occurred during current ICU admission
ARDS	According to the Berlin Criteria, judged by clinicians
Coexisting illness—no (%)	
Ischaemic heart disease	Previous myocardial infarction, previously conducted PCI or CABG, or previous stable or unstable angina pectoris or relevant use of nitrates
Chronic heart failure	Chronic LVEF ≤40% or diagnosed chronic heart failure with preserved LVEF
Active metastatic cancer[a]	Any metastasis from a malignant non-haematological neoplasm, which was not considered eradicated at randomisation
Long-term dialysis	Any renal replacement therapy on a regular basis prior to hospital admission including haemodialysis and peritoneal dialysis
COPD[b]	Defined as previous spirometry in stable phase diagnostic of COPD, or COPD in the anamnesis and daily use of inhaled β_2-adrenergic bronchodilators, anticholinergic bronchodilators, or glucocorticoids
Habitual creatinine >110 mol/L	Known or estimated
Active hematologic malignancy[b]	Defined by the WHO 2017 classification.[12] Is considered active if treated within the last 6 months prior to randomisation
Invasive ventilation	
Patients—no (%)	Patients receiving invasive ventilation
Median TV (IQR)—mL	Last representative measure of tidal volume before randomisation
Median P_{peak} (IQR)—cm of water	Last representative measure of peak pressure before randomisation
Median PEEP (IQR)—cm of water	Last setting before randomisation
NIV or CPAP	
Patients—no (%)	Patients receiving NIV or CPAP
Median PEEP (IQR)—cm of water	Last setting before randomisation

(Continues)

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TABLE 2 (Continued)

Table 2 Baseline characteristics

Parameter	Definition
Open systems	
Patients—no (%)	Patients receiving supplemental oxygen on an open system
Oxygenation	
Median PaO_2 (IQR)—mmHg	Last ABG before randomisation
Median SaO_2 (IQR)—mmHg	Last ABG before randomisation
Median FiO_2[c] (IQR)—mmHg	At the time of the last ABG before randomisation
Median PaO_2:FiO_2 ratio (IQR)	
In all systems	All open systems providing supplemental oxygen therapy
In closed systems	NIV, CPAP, or IMV
Median plasma-lactate (IQR)—mmol/L	Measured on last ABG before randomisation
SOFA score[a,d]	As defined in the SOFA score[13]
Median lowest MAP(IQR)—mmHg	Lowest measurement during the 24 h prior to randomisation
Use of inotropes—no (%)	Number of patients receiving inotropes during the 24 h prior to randomisation
Use of vasopressors	
Patients—no (%)	Number of patients receiving vasopressors during the 24 h prior to randomisation
Median highest dose of norepinephrine (IQR)—μg/kg/min	Highest dose of norepinephrine during the 24 h prior to randomisation

Abbreviations: ABG, arterial blood gas analysis; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CT, computed tomography; ECG, electrocardiography; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; GCS, glasgow coma score; HOT-ICU, handling oxygenation targets in the ICU; HOT-COVID, handling oxygenation targets in COVID-19; ICU, intensive care unit; IMV, invasive mechanical ventilation; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NIV, non-invasive ventilation; PaO_2, arterial partial pressure of oxygen; PCI, percutaneous coronary intervention; PEEP, positive end-expiratory pressure; P_{peak}, peak inspiratory pressure; SaO_2, arterial oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment; TV, tidal volume.

[a]Baseline variable used in the adjusted analyses of the primary and secondary outcomes.

[b]Stratification variable in the HOT-ICU trial.

[c]In open systems the FiO_2 is estimated based on standardised conversion tables (Supplementary 2).

[d]Based on values from the last 24 h prior to randomisation except those concerning respiratory status, where values at randomisation is used. The PaO_2:FiO_2 ratio is based on the last ABG sample prior to randomisation.

[e]Must have led to or occurred during the current hospitalisation.

be presented with 95% CIs, while we will present *p*-values of the tests for interactions with significance levels of .05. As the significance level of the *p*-values for the secondary outcome, the sensitivity analyses, and the subgroup analyses are not adjusted for multiplicity, results should be interpreted cautiously.

2.11 | Statistical analyses

Individual level data from the HOT-ICU and HOT-COVID trials will be appended and analysed in a one-step approach using a GLMM, where the clustering of patients within the trials and sites are accounted for. Sites that are present in both trials are treated as separate clusters in the model. The model will allow for random intercepts and fixed slopes.[15–17] We will adjust the model for each trials' stratification variables: the HOT-ICU trial was stratified for site, presence or absence of chronic obstructive pulmonary disease (COPD), and presence or absence of active haematological malignancy, whereas the HOT-COVID trial was stratified for site only. We will use a VCE(robust) option in Stata as recommended by Cameron and Trivedi[18] as a robust estimator of clustered variance–covariance.[19]

2.11.1 | Primary outcome

The primary dichotomous outcome, 90-day all-cause mortality, will be compared between the intervention groups using a GLMM with a log-link to estimate a relative risk. The adjusted analysis will utilise the same model with adjustment for age, metastatic cancer, admission type, and SOFA-score (Table 2).

2.11.2 | Secondary outcome

The secondary discrete outcome, absolute number of days alive without life-support within 90 days, will be compared between the intervention groups using a GLMM with an identity link to estimate a

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mean difference. The adjusted analysis will utilise the same model with adjustment for age, metastatic cancer, admission type, and SOFA-score (Table 2).

2.11.3 | Subgroup analyses

We will analyse the previously defined subgroups (Table 1) for heterogeneity in the intervention effects for both the primary and secondary outcome, including tests for interaction. The subgroup predictor will have a fixed slope and a random intercept.

2.11.4 | Visualisation of survival time

Survival until 90 days after randomisation will be visualised for both intervention groups using Kaplan–Meier plots based on crude survival data.

2.12 | Handling of missing data

Analyses will be performed without imputation if missingness in data does not exceed 5%. If missingness does exceed 5%, we will perform multiple imputations of missing data using chained equations. The number of imputations needed will be estimated based on a quadratic rule as proposed by Von Hippel.[20]

2.13 | Software

All analyses will be conducted using Stata (StataCorp. 2021. *Stata Statistical Software*. College Station, TX: StataCorp LLC.), with *meglm* (Multilevel mixed-effects generalised linear model) and *stmixed* (Multilevel mixed-effects parametric survival analysis) packages for fitting a multilevel mixed-effects generalised linear model.

3 | DISCUSSION

This individual patient data meta-analysis of the HOT-ICU and HOT-COVID trials will investigate the effects of a lower versus a higher oxygenation target in ICU patients with acute hypoxaemic respiratory failure. It represents the largest compilation of individual patient data on the subject to date. Despite the recent publications of several large clinical trials on the effects of targeted oxygen therapy in the ICU, differences in oxygenation target definition and study design still constrain final recommendations on how to target oxygen supplementation for ICU patients with acute hypoxaemic respiratory failure.[1,4,21] This is especially true for clinically relevant patient groups defined by co-existing illnesses such as COPD and cardiovascular disease.[21,22] With this individual patient data meta-analysis, we aim to address these constrains by utilising individual patient data from two near identical trials to provide re-analyses of clinically relevant outcomes and subgroups with an increased power and less unexplained variation.[23]

3.1 | Choice of statistical models

The primary outcome of 90-day all-cause mortality is dichotomous and will be compared between intervention groups using a GLMM with a log-link combined with a robust variance estimation. This approach was chosen to accommodate the clustered data structure, the dichotomous outcome and the convergence problems typical of binomial log regressions.[18,24,25]

The distribution of the secondary outcome absolute number of days alive without life-support within 90 days is discreet and will range from 0 to 90 days. Based on the results from the HOT-ICU trial, we expect the distribution to be inflated at 0 and 90 days, representing patients dying before getting off life-support, and patients never having received life-support during their ICU admission. This distribution will limit the use of standard count models as Poisson or negative binomial regression. Instead, we will use a GLMM with an identity link combined with robust variance estimation. Despite the non-normal data distribution, the model represents a robust and previously applied approach for estimating a mean difference between the intervention groups, especially given the large sample size.[26,27]

The GLMM models utilises a random intercept reflecting possible differences in the intervention effect on both a trial and site level. The slope of the treatment effect is set as fixed. The interaction between the fixed slope and random intercept will both allow us to investigate differences in the treatment effect between data clusters and between oxygenation targets overall.

3.2 | Strengths and limitations

Despite the similarities of the HOT-ICU and HOT-COVID trials, the two trials are fundamentally separate units conducted at different time points and with different, albeit comparable, study populations with different triggers for development of acute hypoxaemic respiratory failure. Further, both are multi-centre trials with trial sites spanning a large part of Europe. Consequently, data should not be treated as independent since we would expect differences on both a trial and site level that could influence the observed intervention effect. Apparent examples are local differences in ICU treatment, ICU monitoring equipment, workflow, composition of the ICU population, standard oxygenation strategy prior to the trials, and nurse-to-patient staffing ratios. If this is not addressed, we risk inflating probability estimates, which could result in a mischaracterisation of the investigated relationship between targeted oxygen therapy and the selected outcomes. We will acknowledge this by pooling trial data in a one-step procedure utilising a GLMM that allow for a hierarchical data structure with data clustered at both a trial and a site level. Further, the GLMM facilitates an analysis of how individual patient traits might

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affect the intervention effect on both the primary and secondary outcome.

We have chosen to present results without adjusting CIs and significance levels of *p*-values for multiplicity in the primary outcome, the secondary outcomes, and the tests for interactions in the subgroups. This approach was preferred due to the clearly stated hierarchy of the outcomes and to provide a simple, transparent presentation of data combined with a recommendation to interpret the significance of the secondary outcome, the adjusted analyses, and the tests for interaction cautiously due to the inherent risk of spurious findings when conducting multiple comparisons.[28] Since 14 subgroups are analysed for two outcomes with an alpha level of .05, we could expect at least one analysis to present a significant *p*-value due to chance if data were truly independent. Therefore, the subgroup analyses are strictly explorative. To facilitate correct interpretation of the results, we here clearly define the number of subgroups, their expected direction of effect, and present a plan for assessing the credibility of subgroup results using the ICEMAN tool.[11,29]

4 | CONCLUSION

The HOT-ICU and HOT-COVID trials are two of the largest randomised clinical trials that have investigated targeted supplemental oxygen for patients admitted to an ICU with acute hypoxemic respiratory failure. The trials have a substantial overlap in design, but individual patient data cannot be pooled indiscriminately. Here we present a protocol with a statistical analysis plan for analysing clinically relevant outcomes and subgroups utilising a pooled complete dataset while accounting for data clustering at a trial and site level.

AUTHOR CONTRIBUTIONS

Frederik Mølgaard Nielsen drafted the manuscript for this paper in close collaboration with Thomas Lass Klitgaard, Niels Henrik Bruun, Morten Hylander Mølle, Olav Lilleholt Schjørring and Bodil Steen Rasmussen. All authors made substantial contributions in defining the statistical analyses and study design. All authors have read and approved the final manuscript. Frederik Mølgaard Nielsen is the coordinating investigator of the HOT-COVID trial. Thomas Lass Klitgaard was coordinating investigator for both the HOT-ICU trial and the HOT-COVID trial. Olav Lilleholt Schjørring was coordinating investigator for the HOT-ICU trial. Bodil Steen Rasmussen is the principal investigator and sponsor for both the HOT-ICU trial and the HOT-COVID trial.

ACKNOWLEDGEMENTS

All authors declare no conflicts of interest.

FUNDING INFORMATION

The HOT-ICU trial was funded by the Innovation Fund Denmark (4108-00011A), the Novo Nordisk Foundation, the Obel Family Foundation, Regionernes Medicinpulje, the Danish Society of Anaesthesiology and Intensive Care Medicine, and the Intensive Symposium Hindsgavl. The HOT-COVID trial was funded by the Danish Ministry of Higher Education and Research (0238-00004B), and the Novo Nordisk Foundation. Funding sources had no influence on trial designs, trial conduct, data collection, data analysis, result interpretation, or the scientific content of the present protocol.

DATA AVAILIABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

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

How to cite this article: Nielsen FM, Klitgaard TL, Bruun NH, Møller MH, Schjørring OL, Rasmussen BS. Lower or higher oxygenation targets for acute Hypoxaemic respiratory failure: Protocol for an individual patient data meta-analysis. *Acta Anaesthesiol Scand*. 2023;67(6):811-819. doi:10.1111/aas.14220

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