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RESEARCH ARTICLE

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Long-term cognitive and pulmonary functions following a lower versus a higher oxygenation target in the HOT-ICU and HOT-COVID trials: A protocol update

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Abstract

Background: The Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial was a multicentre, randomised, parallel-group trial of a lower oxygenation target (arterial partial pressure of oxygen [PaO_2] = 8 kPa) versus a higher oxygenation target (PaO_2 = 12 kPa) in adult ICU patients with acute hypoxaemic respiratory failure; the Handling Oxygenation Targets in coronavirus disease 2019 (HOT-COVID) tested the same oxygenation targets in patients with confirmed COVID-19. In this study, we aim to evaluate the long-term effects of these oxygenation targets on cognitive and pulmonary function. We hypothesise that a lower oxygenation target throughout the ICU stay may result in cognitive impairment, whereas a higher oxygenation target may result in impaired pulmonary function.

Methods: This is the updated protocol and statistical analysis plan of two pre-planned secondary outcomes, the long-term cognitive function, and long-term pulmonary function, in the HOT-ICU and HOT-COVID trials. Patients enrolled in both trials at selected Danish sites and surviving to 1 year after randomisation are eligible to participate. A Repeatable Battery for the Assessment of Neuropsychological Status score and a full-body plethysmography, including diffusion capacity for carbon monoxide, will be obtained. The last patient is expected to be included in the spring of 2024.

Conclusion: This study will provide important information on the long-term effects of a lower versus a higher oxygenation target on long-term cognitive and pulmonary functions in adult ICU patients with acute hypoxaemic respiratory failure.

KEYWORDS
clinical trial, critical care outcomes, ICU, oxygen inhalation therapy

1 | INTRODUCTION

Cognitive impairment and pulmonary dysfunction have been described as longstanding complications in intensive care unit (ICU) survivors.[1] A low arterial partial pressure of oxygen (PaO_2) has been associated with poor cognitive performance,[2] while concerns about higher oxygenation targets being possibly disadvantageous in terms of pulmonary function have been raised.[3] However, the evidence on the long-term effects of oxygen therapy in adult ICU survivors is still very uncertain.[4]

The Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial investigated a lower versus a higher oxygenation target in adult patients acutely admitted to ICU with hypoxaemic respiratory failure,[5] and the Handling Oxygenation Targets in coronavirus disease 2019 (HOT-COVID) trial tested similar interventions in hypoxaemic patients with a confirmed COVID-19 infection.[6] In the present study, we aim to evaluate the effects of the two oxygenation targets on cognitive and pulmonary functions in survivors 1 year after randomisation in the HOT-ICU or HOT-COVID trials. We hypothesise that the lower oxygenation target results in long-term cognitive impairment, whereas the higher oxygenation target results in impaired long-term pulmonary function.

2 | METHODS

2.1 | Study design

This is the updated protocol and statistical analysis plan for a sub-study of the HOT-ICU and HOT-COVID trials evaluating the two pre-planned secondary long-term outcomes; cognitive function and pulmonary function,[5–7] 1 year after randomisation in survivors included at selected Danish sites. This is an amendment to the previously published protocol for these outcomes in the HOT-ICU trial.[8] In the following, we will only consider the elements that have been changed from the primary version of the protocol.[8]

This protocol amendment was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.[9] An updated SPIRIT 2013 checklist is presented in Appendix S1.

2.2 | The Danish cohort of the HOT-ICU and HOT-COVID trials

The HOT-ICU and HOT-COVID trials were both investigator-initiated, pragmatic, multi-centre, randomised, parallel-group trials of a lower versus a higher oxygenation target in adult patients acutely admitted to the ICU with severe hypoxaemic respiratory failure, with outcome-assessor blinding of the present long-term cognitive and pulmonary outcomes. Inclusion criteria defining severe hypoxaemic respiratory failure were provision of at least 10 L of oxygen per minute in an open system in both trials, or a fraction of inspired oxygen (FiO_2) of at least 0.50 in a closed system in the HOT-ICU trial, but with no limits for FiO_2 in closed systems in the HOT-COVID trial.[5,6] Additionally, the HOT-COVID trial required a confirmed severe acute respiratory syndrome coronavirus 2 infection.[6] Full lists and definitions of inclusion and exclusion criteria can be found elsewhere.[5–7] Patients were randomised 1:1 within 12 h of ICU admission to either a PaO_2 target of 8 kPa (lower oxygenation target) or 12 kPa (higher oxygenation target) during ICU admission up to a maximum of 90 days after randomisation, including ICU readmissions. The HOT-ICU trial was performed in 35 ICUs across 7 countries, and the HOT-COVID trial was performed in 11 ICUs across 3 countries. The Danish trial cohorts consist of 2332 patients in the HOT-ICU trial, and of 593 patients in the HOT-COVID trial, respectively.

2.3 | Approvals and registrations

The HOT-COVID trial was approved as an amendment to the HOT-ICU trial. Thus, approvals for both trials are identical as follows: from the Danish Health and Medicines Agency (AAUH-ICU-01), the Committee on Health Research Ethics in the North Denmark Region (N-20170015), the Danish Data Protection Agency (2017-055), all required authorities in participating countries, and the European clinical trials database (EudraCT number 2017-000632-34). Both trials were prospectively registered at Clinicaltrials.gov (Identifier: NCT03174002 for the HOT-ICU trial; NCT04425031 for the HOT-COVID trial).[6,7] Additional details on both trials are available elsewhere.[5–7]

2.4 | Study population and 1-year cognitive and pulmonary follow-up

Patients enrolled in the HOT-ICU and HOT-COVID trials at selected Danish sites and surviving until 1 year after randomisation are eligible to participate. The inclusion criteria are the following: (1) included in the HOT-ICU or HOT-COVID trials; (2) able to speak and understand the Danish language; (3) informed consent to participate in the long-term evaluations of cognitive and lung functions. Patients will be excluded from the study if they meet any of the following criteria: (1) more than 20 months since inclusion; (2) consent not obtainable according to national regulations; (3) body weight above 150 kg (only an exclusion criterion for the lung function test).

2.5 | Outcome measures

The two pre-planned long-term outcomes covered in this study are:

1. A global cognitive score obtained from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),[10] which is a comprehensive test battery for the neuropsychological status consisting of 12 subtests designed to produce a global cognitive score and index scores for five different cognitive

domains (immediate memory; delayed memory; attention; language; and visuospatial/constructional abilities).
2. A full-body plethysmography with measurement of pulmonary diffusion capacity for carbon monoxide as the inactive tracer gas mixed with oxygen and nitrogen. The value obtained corresponds to the diffusing capacity for carbon monoxide (DLCO).[11]

Exploratory outcomes include the five cognitive domains of the RBANS, and the following measurements of dynamic and static lung function: (a) forced expiratory volume in the first second (FEV_1), (b) forced vital capacity (FVC), (c) the ratio between FEV1 and FVC (FEV_1/FVC), (d) total lung capacity (TLC), (e) inspiratory capacity (IC), (f) ratio between IC and TLC (IC/TLC), (g) residual volume, and (h) intrathoracic gas volume.

2.6 | Statistics

We will conduct all analyses according to the intention-to-treat principle among 1-year survivors unless specified otherwise.[12] The intention-to-treat population includes all randomised Danish patients at selected sites surviving to 1 year after randomisation, except where follow-up data cannot be obtained due to loss to follow-up, for example, due to withdrawal of consent according to national regulations.[13–15] Individual patient-level data from the two trials will be appended and analysed in a one-step approach using a linear mixed model, accounting for clustering of patients within the trials and sites. Specifically, we will include a random effect for trial and sites. We will not adjust for other stratification variables as these were not similar in the two trials. We will use a robust estimator of clustered variance–covariance[16]; preferably a VCE(robust)[17] option in Stata. However, if more than 20 iterations are required to obtain convergence, a VCE(cluster)[17] will be used instead to avoid overfitting. Additionally, we will perform supplemental analyses of all outcomes in each trial separately using a linear regression adjusted for each trial's stratification variables (site, presence or absence of chronic obstructive pulmonary disease, and presence or absence of active haematological malignancy in the HOT-ICU trial; site in the HOT-COVID trial) and a robust estimator of clustered variance–covariance, as described above. All results will be presented as mean differences with 95% confidence interval and a *p*-value below 0.05 will be considered statistically significant. All statistical analyses will be conducted using Stata version 17, STATA Nordic.

We will report the RBANS scores (comprising the global cognitive score and the five index scores) in each intervention group, stratified by the age-adjusted mean and standard deviation in cognitive test performance (above normal: >115 points; normal: between 85 and 115 points; mild impairment: between 70 and 84 points; moderate impairment: between 55 and 69 points; severe impairment: <54 points)[10]; DLCO will be presented as the percentage of the predicted values in each intervention group categorised by severity (normal:> 80%; mildly impaired: from 60% to 80%; moderately impaired: from 40% to 59%; severely impaired:<40%).[18] Finally, to quantify the proportions of patients with obstructive or restrictive patterns in the exploratory pulmonary function outcomes, we will report proportions of patients with an FEV_1/FVC ratio below 70% as indicative of obstructive pulmonary disease,[19] and an FVC below 80% or a TLC below 90% as indicative of restrictive pulmonary disease.[20,21]

2.7 | Evaluation of sample representativeness

In order to evaluate if our sample is representative of the entire trial population alive at 1 year, we will compare the baseline variables and non-mortality outcomes at 90 days (i.e., serious adverse events in the ICU, days alive without life-support in the ICU, days alive and out of hospital), and 1 year (i.e., EuroQol visual analogue scale score)[22] between the subpopulation included in this study and the remaining combined trial cohort alive at 1 year from randomisation.[6,7] We will use a chi-squared test for categorical data and a parametric or non-parametric test for continuous data, as appropriate.

3 | DISCUSSION

This 1-year follow-up sub-study of the HOT-ICU and HOT-COVID trials will provide new important information on cognitive and pulmonary long-term outcomes following lower versus higher oxygenation targets in acutely ill patients with hypoxaemic respiratory failure admitted to the ICU. Thus far, only one randomised clinical trial (RCT) investigating two oxygenation strategies has performed cognitive follow-up at 180 days post-randomisation,[23] whereas long-term pulmonary function has never been studied in RCTs exploring lower versus higher oxygenation strategies, except in a very small COPD population.[24] Since the COVID-19 pandemic has significantly affected the 1-year follow-up inclusion rate of the HOT-ICU trial, we decided to analyse and present the 1-year pulmonary and cognitive outcomes for both trials in combination.

4 | STATUS

The 1-year follow-up of the HOT-ICU trial was completed in October 2021 with a total of 216 patients included in this sub-study. The 1-year follow-up of the HOT-COVID trial is currently ongoing and the last patient is expected to be assessed during spring 2024.

AUTHOR CONTRIBUTIONS

EC and BSR wrote the first draft of the article. All authors made substantial contributions to the article and provided important scientific input and read plus approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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