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RESEARCH ARTICLE

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Handling oxygenation targets in ICU patients with COVID-19—Protocol and statistical analysis plan in the HOT-COVID trial

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Abstract

Background: Coronavirus disease (COVID-19) primarily affects the lungs and lower airways and may present as hypoxaemic respiratory failure requiring admission to an intensive care unit (ICU) for supportive treatment. Here, supplemental oxygen remains essential for COVID-19 patient management, but the optimal dosage is not defined. We hypothesize that targeting an arterial partial pressure of oxygen of 8 kPa throughout ICU admission is superior to targeting 12 kPa.

Methods: The Handling Oxygenation Targets in ICU patients with COVID-19 (HOT-COVID) trial, is an investigator-initiated, pragmatic, multicentre, randomized, parallel-group trial comparing a lower oxygenation target versus a higher oxygenation target in adult ICU patients with COVID-19. The primary outcome is days alive without life-support (use of mechanical ventilation, renal replacement therapy or vasoactive therapy) at day 90. Secondary outcomes are 90-day and 1-year mortality, serious adverse

events in the ICU and days alive and out of hospital in the 90-day period, health-related quality-of-life at 1 year, and health economic analyses. One-year follow-up of cognitive and pulmonary function is planned in a subgroup of Danish patients. We will include 780 patients to detect or reject an absolute increase in days alive without life-support of 7 days with an α of 5% and a β of 20%. An interim analysis is planned after 90-day follow-up of 390 patients.

Conclusions: The HOT-COVID trial will provide patient-important data on the effect of two oxygenation targets in ICU patients with COVID-19 and hypoxia. This protocol paper describes the background, design and statistical analysis plan for the trial.

KEYWORDS
COVID-19, hypoxia, intensive care units, oxygen

1 | INTRODUCTION

Since its emergence in November 2019, the severe acute respiratory syndrome corona-virus-2 (SARS-CoV-2) has spread across the globe and caused an on-going pandemic.[1] Currently, more than 181,000,000 confirmed cases of infection have been recorded and more than 3,900,000 people have died.[2]

The disease caused by SARS-CoV-2 has been named coronavirus disease 2019 (COVID-19)—in its most severe form it is characterized by pneumonia leading to profound hypoxia and a clinical presentation resembling acute respiratory distress syndrome (ARDS).[3,7,8] Admission to an intensive care unit (ICU) is required in 1–16% of cases[4-6] and the reported a mortality rate for the most severely affected ranges from 35 to 46%.[3,9,10,11]

Administration of supplemental oxygen therapy is essential for management of severe COVID-19.[12] Whereas supplementary oxygen therapy is categorized as a medical drug in most of the world, its correct dosage remains a much-contested issue.[13-15] Current treatment strategies aim to avoid life-threatening hypoxaemia and tend to apply a large margin of safety[16-18] and evidence for systematic strategies of oxygenation titrating is limited.[19] This is important as hyperoxaemia has potential deleterious effects through systemic vasoconstriction,[20] pulmonary absorption atelectasis[21] and production of free radicals causing oxidative stress.[22]

The global health crisis caused by SARS-CoV-2 combined with the essential role of supplemental oxygen for managing the disease makes optimization of oxygen dosage pertinent.[8] Currently, no evidence-based recommendations are available. Furthermore, recent examples of unstable oxygen supplies in numerous countries demonstrate the importance of determining the safety and effectiveness of a lower oxygenation target for COVID-19 patients in order to help ensure effective utilization.

We aim to compare the effects of targeting a partial pressure of arterial oxygen (PaO_2) of 8 kPa versus targeting a PaO_2 of 12 kPa in ICU patients with COVID-19 and hypoxaemic respiratory failure and hypothesize that targeting a PaO_2 of 8 kPa increases the number of days alive without life-support in 90 days after randomization when compared to targeting a PaO_2 of 12 kPa.

2 | METHODS

This publication represents the protocol and detailed statistical analysis plan for the Handling Oxygenation Targets in COVID-19 (HOT-COVID) trial. The HOT-COVID trial is an amendment to the HOT-ICU trial.[23-25] The main HOT-ICU protocol applies to all patients included in the HOT-COVID trial except in respect to any protocol alterations described in this publication.[23,24]

3 | TRIAL DESIGN

The HOT-COVID trial is an investigator-initiated, pragmatic, international, multicentre, randomized, outcome-assessor blinded, parallel-group trial. Adult ICU patients with confirmed COVID-19 and hypoxaemic respiratory failure will be allocated 1:1 to a lower oxygenation target (PaO_2 of 8 kPa) or a higher oxygenation target (PaO_2 of 12 kPa). All screening and randomization procedures are conducted as in the Handling Oxygenation Targets in the ICU (HOT-ICU) trial.[23-25] Randomization is centralized and web-based according to concealed computer-generated allocation sequence lists stratified for trial site and with permuted varying block sizes. The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.[26] The SPIRIT checklist is presented in the Supplement.

4 | APPROVALS, REGISTRATION AND ETHICS

The HOT-COVID trial is approved as an amendment to the HOT-ICU trial by 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), and by all required authorities in participating countries. It is registered at ClinicalTrials.gov (Identifier: NCT04425031) and in the European clinical trials database (EudraCT, Identifier: 2017-000632-34). The trial is externally

monitored according to the Good Clinical Practice (GCP) standards, it will adhere to the Helsinki Declaration,[27] and patients will be enrolled after consent to participate has been obtained as according to national regulations.

5 | SETTING

ICU's in university and non-university hospitals in Denmark, Norway and Switzerland. A comprehensive list of participating sites can be found at ClinicalTrials.gov (identifier: NCT04425031). All trial sites are familiar with conducting large-scale randomized clinical trials, are part of the Collaboration for Research in Intensive Care (CRIC) network and have previously participated in the HOT-ICU trial.

6 | INCLUSION CRITERIA

Patients are screened for inclusion into the HOT-COVID trial if they fulfil the following criteria within 12 h of ICU admission:

1. Acutely admitted to the ICU AND
2. Age ≥18 years AND
3. Polymerase chain reaction confirmed SARS-CoV-2 infection leading to or during current hospital admission AND
4. Supplemental oxygen with a flow of at least 10 L oxygen per minute in an open system or invasive mechanical ventilation, non-invasive mechanical ventilation (NIV) or continuous positive airway pressure (CPAP) independent of the fraction of inspired oxygen (FiO_2) AND
5. Expected to receive supplemental oxygen for at least 24 h in the ICU AND
6. An arterial line for PaO_2 monitoring

7 | EXCLUSION CRITERIA

Patients who fulfil one or more of the criteria below will be excluded from the HOT-COVID trial.

1. Cannot be randomized 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 or performed 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 randomized into the HOT-ICU or HOT-COVID trials

8 | INTERVENTIONS

Patients will be randomized to a target PaO_2 of either 8 kPa or 12 kPa. The oxygenation target applies throughout the entire ICU stay including any readmissions for up to 90 days after randomization. In both intervention groups, the target PaO_2 is achieved by carefully titrating the FiO_2 from 0.21 to 1.00 guided by PaO_2 values from arterial blood gas analyses (ABGs). Continuous measurements of peripheral oxygen saturation (SpO_2) are used to guide the targeted oxygenation strategy between ABGs. Deviation above the allocated oxygenation target will only be allowed in case of an $FiO_2 = 0.21$, while deviation below the oxygenation target will only be allowed in case of an $FiO_2 = 1.00$ or difficulties in achieving target paO2 during respirator weaning. The trial design is pragmatic; all treatment decisions including type of oxygen delivery system and ventilator settings except FiO_2 is at the discretion of the treating clinicians.

9 | WITHDRAWAL AND DISCONTINUATION OF TRIAL INTERVENTION

Patients will be withdrawn from the trial if informed consent is retracted or not given in accordance with national regulations. Furthermore, patients are withdrawn from the trial if they encounter a suspected unexpected serious adverse reaction (SUSAR). Of note, no SUSARs were reported in the HOT-ICU trial.[25] In case of withdrawal, data collection will be continued if consent for this is given.

10 | OUTCOME MEASURES

The primary outcome in the HOT-COVID trial is the absolute number of days alive without life support, that is, mechanical ventilation, circulatory support or renal replacement therapy in 90 days after randomization. Mechanical ventilation is defined as either invasive mechanical ventilation, NIV or CPAP. Intermittent CPAP is not considered mechanical ventilation. Circulatory support is defined as continuous infusion of a vasoactive or inotropic drug.

Secondary outcomes include: (a) 90-day all-cause mortality; (b) number of patients with one or more serious adverse event (SAE) in the ICU within 90 days from randomization defined as a new episode of myocardial ischaemia, a new episode of intestinal ischaemia, a new episode of shock or a new ischaemic stroke; (c) absolute number of

days alive and out of hospital within 90 days after randomization; (d) 1-year all-cause mortality; (e) health related quality of life at 1-year follow-up measured using EuroQol 5 dimensions 5 level questionnaire including EQ visual analogue scale (EQ-5D-5L); (f) cognitive function at 1-year follow-up measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at 1-year follow-up at selected sites; (g) pulmonary function at one year follow-up at selected sites; and (h) a health economic cost-benefit analysis. The detailed outcome definitions are specified in the Supplement.

11 | SAMPLE SIZE AND POWER ESTIMATIONS

Based on available data on mortality and the clinical experience available in spring 2020 for patients with severe COVID-19, it was assumed that 40% of patients die while on life-support in the ICU.[28] These patients will have 0 days alive without life-support. Furthermore, it was estimated that survivors receive an average of 14 days of life-support. This yields an average 45.6 days alive without life-support out of 90 days in the 12 kPa control group. We estimated that targeting a PaO_2 of 8 kPa would reduce 90-day mortality with 20% and reduce the number of days with life-support with 10% in survivors.

This yields an average 52.6 days alive without life-support in the 8 kPa lower oxygenation group. Applying a power of 80% and an alpha-level of 5%, a total of 780 patients are needed to detect or reject the absolute difference of 7 days alive without life-support between groups.

12 | REGISTERED VARIABLES

The registered variables at baseline, daily during ICU-stay, at 90-day follow-up, and at 1-year follow-up in the HOT-COVID trial are similar to registrations in the HOT-ICU trial.[24] They are available in the Supplement. Data will be collected in an electronic data form.

13 | GENERAL ANALYTICAL PRINCIPLES

All analyses will be conducted according to the intention-to-treat principle[29] with the exception of the per-protocol sensitivity analyses. The intention-to-treat population includes all randomized patients except those where follow-up data cannot be obtained due to withdrawal of consent according to national regulations.[30-32] All results will be presented with 95% confidence intervals (CIs) unless specified otherwise. All tests for significance will be two-sided, a *p*-value below .05 will be considered statistically significant unless specified otherwise. CIs adjusted for the multiple secondary outcomes not including the null effect will be considered statistically significant. We will adopt the five step procedure as described by Jakobsen et al when assessing the results.[33]

14 | TRIAL PROFILE

As according to the consolidated standard of reporting trials (CONSORT),[34] the flow of patients will be presented in a diagram including the number of patients assessed for eligibility equal to all patients fulfilling all inclusion criteria, the number of exclusions with reasons for exclusions, and the final number of patients included in the analysis.

15 | MISSING DATA

A complete case analysis without imputation of missing values will be performed if less than 5% of the data are missing in any primary or secondary outcome analysis. If missing data exceed 5%, the need of imputation will be evaluated, and multiple imputation of missing data will be conducted, in similar way as specified for the HOT-ICU trial.[24] Further details are available in the Supplement.

16 | STATISTICAL ANALYSES

16.1 | Primary outcome

The primary outcome in the HOT-COVID trial is the absolute number of days alive without life support in the 90-day period. It will be compared between the intervention groups using a generalized linear model or a semi-parametric test, adjusted for the stratification variable site. We will use Poisson distribution or alternately negative binomial distribution for the generalized linear model.[35] If assumptions are not met for these distributions, we will use the nonparametric van Elteren test to analyse the data.[36] Evaluation of significance of the result will be based on the *p*-value from the generalized linear model or the van Elteren test. We will also report unadjusted absolute differences with 95% CIs based on bootstrap procedures.

An adjusted secondary analysis will be conducted, adjusting for the stratification variable site as well as for important prognostic baseline factors being age, active haematological malignancy, known chronic obstructive pulmonary disease (COPD), active metastatic cancer and Sequential Organ Failure (SOFA) score, analysed using a generalized linear model similar to the primary analysis if assumptions for this is met. If data does not fulfil the assumptions for the parametric models, we will apply a linear model for the, mean regardless of the non-parametric data distributions to allow for the multiple adjustments required.

Furthermore, differences between each of the individual components of the primary outcome, that is, days without mechanical ventilation, circulatory support or renal replacement therapy, will be investigated in explorative analyses using a generalized linear model or nonparametric test, adjusted for the stratification variable site.

Sensitivity analyses of the primary outcome measure will be conducted in per-protocol populations as described for the HOT-ICU

trial.[23] The primary sensitivity analysis in the HOT-COVID trial will be all randomized patients, except patients with a major protocol violation (MPV)[23] in two or more consecutive 12-h intervals, corresponding to the patient being at least 24 h off target; only consecutive MPVs that deviate to the same side (either above or below the allocated oxygenation target) will exclude the participant.

16.2 | Secondary outcomes

The dichotomous secondary endpoints of all-cause mortality at day 90 and 1 year after randomization, and one or more SAEs during ICU admission will be compared using a generalized linear model with a log-link and binomial error distribution adjusted for site for the relative risk; and using a generalized linear model with an identity-link and binomial error distribution for the absolute difference. Absolute differences and risk ratios with multiplicity adjusted CIs will be reported. The crude all-cause mortality will be illustrated using Kaplan-Meier plots and difference between groups will be assessed using a Cox proportional hazards model adjusted for site.

The continuous secondary outcomes of (a) absolute number of days alive out of hospital in the 90-day period, (b) the EQ visual analogue scale score of the EQ-5D-5L at 1-year follow-up, (c) the global cognition score of the RBANS test at 1-year follow-up, and (d) the carbon monoxide diffusion capacity of the pulmonary function test at 1-year follow-up will be analysed using a generalized linear model or a nonparametric test with adjustment for site. Non-survivors will be assigned the lowest possible EQ visual analogue scale score of 0.

In all secondary outcomes, adjustments of the CIs due to multiplicity will be performed according to the procedure specified by Jakobsen et al.[37] With six separate secondary outcomes (the 90-day and 1-year mortalities are considered one outcome in the adjustments, as they are highly mutually dependent), the multiplicity adjusted *p*-values will be below .014 to preserve a family wise error rate below 5%, equivalent of an adjusted CI of 98.6%. Thus, if the adjusted 98.6% CIs for the multiple secondary outcomes does not include the null effect, the results will be considered statistically significant. *p*-values below .014 will be considered definitely significant and *p*-values above .014 will be considered definitely non-significant. *p*-values below .05 but above .014 will be considered possibly significant but not confirmative.

The proportions of patients with the separate SAEs during ICU stay from the composite SAE endpoint will be reported as supplementary outcomes, analysed using a generalized linear model with a log-link and binomial error distribution with adjustment for the stratification variable site and reported as exploratory results.

The EQ-5D-5L scores from level 1 (best) to level 5 (worst) in each of the five dimensions will be compared using a generalized linear model or a non-parametric test with adjustment for stratification variable site and will be reported as exploratory results. Non-survivors will be assigned the worst possible score of 5 in all EQ-5D-5L dimensions. Exploratory supplementary analyses omitting non-survivors of the EQ visual analogue scale score and of scores in each of the five EQ-5L-5L dimensions will be conducted.

All exploratory results will be reported with 95% CIs.

16.3 | Subgroup analyses

We will assess the heterogeneity of intervention effects of the primary outcome in the HOT-COVID trial in five pre-planned subgroups: (a) in patients with known COPD at randomization (yes/no), we hypothesize a greater increase in days alive without life support at day 90 in the 8 kPa PaO_2 target group in patients with known COPD; (b) in patients with active haematological malignancy (yes/no), we hypothesize a greater increase in days alive without life support at day 90 in the 8 kPa PaO_2 target group in patients with active haematological malignancy; (c) in patients with shock at randomization (yes/no), based on as of yet unpublished results from the HOT-ICU trial we hypothesize a decrease in days alive without life support at day 90 in the 8 kPa PaO_2 target group in patients with shock; and (d) according to baseline PaO_2/FiO_2 ratio (<13.3 kPa; ≥13.3 to <26.7 kPa; ≥26.7 to <40.0 kPa; and ≥40.0 kPa); we hypothesize a successively greater increase in days alive without life support at day 90 in the 8 kPa PaO_2 target group with lower PaO_2/FiO_2 ratios. In the subgroup analyses, only the primary outcome will be evaluated. Comparisons will be conducted using a generalized linear model or a nonparametric test as specified for the primary analysis, adjusted for the stratification variable site. We will apply tests of interaction for all subgroups in the analyses, if data are non-parametric, a general linear model for the mean will be applied for this.

17 | PATIENT CHARACTERIZATION, ICU TREATMENT AND SEPARATION OF INTERVENTION GROUPS

In the HOT-COVID trial, the baseline variables, the conducted ICU treatment, and the oxygenation target separation in the intervention groups will be reported in similar manner as specified for the HOT-ICU trial.[24]

18 | DATA MONITORING AND SAFETY COMMITTEE (DMSC) AND INTERIM ANALYSES

The trial will be monitored by an independent DMSC during the entire trial period. The DMSC will adhere to the predefined Charter for the DMSC (Supplement) and will operate comparably to the DMSC in the HOT-ICU trial.[23,25]

An interim analysis applying the Lan DeMets' stopping criteria[38] is planned to be conducted when the initial 390 patients, corresponding to 50% of the study population, have completed their

90-day follow-up. The DMSC can request unplanned interim analyses at any time during the trial period.

19 | DISCUSSION

SARS-CoV-2 has caused a strain on health care systems and especially ICUs worldwide. Patients with COVID-19 admitted to the ICU are primarily affected by lung tissue injury leading to hypoxia, and treatment is presently limited to supportive care with administration of supplemental oxygen therapy being of critical significance for patient survival. Furthermore, reported pathophysiological differences between COVID-19 related lung injury and ARDS complicates using available data on oxygenation strategies for the critically ill to optimize COVID-19 treatment.[8] Presently no evidence-based recommendations are available for oxygen dosage when treating patients with severe COVID-19, while the Surviving Sepsis Guidelines recommends targeting a SpO2 of 92–96% based on expert opinions.[39]

As of yet unpublished data concerning a sub-group analysis of 110 patients with COVID-19 in the HOT-ICU trial indicated that targeting an arterial partial pressure of oxygen (PaO_2) of 8 kPa compared with targeting a PaO_2 of 12 kPa throughout ICU admission increased the percentage of days alive without life-support. This result however is inconclusive due to the limited size of the subpopulation and furthermore, other clinical outcomes including mortality were not different between groups. The present study seeks to expand on these initial findings with the feasibility of the study design and the safety of the clinical intervention validated by the results from the completed HOT-ICU trial and its COVID-19 subpopulation.[23,24]

To ensure the validity of the obtained results, the trial will utilize a pragmatic, randomized, parallel-group design with patient inclusion and treatment performed at multiple sites. Further, the trial is externally monitored by GCP units to certify that national and international regulations are met.

The complete trial protocol and statistical analysis plan will be submitted and preferably published before the 90-day follow-up of the 390th patient to ensure methodical transparency and safety, also for the interim analysis.

The inclusion rate, age and disease severity of patients with COVID-19 admitted to ICUs with hypoxaemic respiratory failure will most likely fluctuate over time due to the introduction of vaccinations, improved treatment protocols and emergence of new virus variants. The potential changes in the study population over time can prolong the study duration and possibly influence the subgroup analyses, but the randomized design of the study will ensure a valid assessment of the primary and secondary outcomes.

Finally, patients randomized into the HOT-COVID trial are available for co-enrolment into other clinical trials provided that the interventions do not conflict. Unpredicted interactions between interventions can in principle occur; these will be addressed through secondary sensitivity analyses. However, co-enrolment ensures that knowledge can be generated more efficiently and prohibiting patients from participating in more than one study infringes on their autonomy and denies them the potential clinical benefit gained from participation.

20 | PERSPECTIVES

The HOT-COVID trial is currently the only large randomized clinical trial investigating targeted supplemental oxygen for patients with hypoxia due to COVID-19. The results will be valuable in assessing the optimal dosage of supplemental oxygen for treating severe COVID-19 in an ICU setting.

TRIAL STATUS

The first randomization was performed on the 25th of August 2020 and the trial is currently recruiting at 10 active sites. At the 1st of July 2021, 426 patients have been randomized and we are awaiting 90-day follow-up of patient number 390 for the planned interim analysis. The last patient is expected to be included medio 2022. The current protocol version is the amended HOT-ICU protocol version 2.2 of the 14th August 2020.

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AUTHOR CONTRIBUTIONS

FMN and BSR drafted the manuscript for this paper in close collaboration with TLK, OLS, AP and TL. Furthermore, EC, SRA, ASA, LMP, ACB, MHB, SI, BAB, JHL, TG and TH all made substantial contributions to the manuscript and provided important scientific input. The HOT-COVID trial was designed by the members of the HOT-COVID Management Committee consisting of TLK, OLS, BSR, AP and TL. FMN functions as coordinating investigator for the HOT-COVID trial.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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