



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Long-term cognitive and pulmonary functions following a lower versus a higher oxygenation target in the HOT-ICU trial

protocol and statistical analysis plan

Crescioli, Elena; Riis, Jens Ø.; Weinreich, Ulla M.; Jensen, Jens Ulrik S.; Poulsen, Lone M.; Brøchner, Anne C.; Lange, Theis; Perner, Anders; Klitgaard, Thomas L.; Schjørring, Olav L.; Rasmussen, Bodil S.

Published in:

Acta Anaesthesiologica Scandinavica

DOI (link to publication from Publisher):

[10.1111/aas.13995](https://doi.org/10.1111/aas.13995)

Publication date:

2022

Document Version

Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Crescioli, E., Riis, J. Ø., Weinreich, U. M., Jensen, J. U. S., Poulsen, L. M., Brøchner, A. C., Lange, T., Perner, A., Klitgaard, T. L., Schjørring, O. L., & Rasmussen, B. S. (2022). Long-term cognitive and pulmonary functions following a lower versus a higher oxygenation target in the HOT-ICU trial: protocol and statistical analysis plan. *Acta Anaesthesiologica Scandinavica*, 66(2), 282-287. <https://doi.org/10.1111/aas.13995>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

DR ELENA CRESCIOLI (Orcid ID : 0000-0002-8267-7634)

DR OLAV LILLEHOLT SCHJØRRING (Orcid ID : 0000-0002-7749-6003)

DR BODIL STEEN RASMUSSEN (Orcid ID : 0000-0003-2190-145X)

Article type : Research Article

Long-term cognitive and pulmonary functions following a lower versus a higher oxygenation target in the HOT-ICU trial – protocol and statistical analysis plan.

Elena Crescioli^{1,2}, Jens Østergaard Riis³, Ulla Møller Weinreich^{2,4}, Jens Ulrik Stæhr Jensen⁵, Lone Musaeus Poulsen⁶, Anne Craveiro Brøchner⁷, Theis Lange⁸, Anders Perner⁹, Thomas Lass Klitgaard^{1,2}, Olav Lilleholt Schjørring^{1,2}, Bodil Steen Rasmussen^{1,2}

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

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

³ Departments of Neurology and Neurosurgery, Aalborg University Hospital, Aalborg, Denmark

⁴ Department of Respiratory Medicine, Aalborg University Hospital, Aalborg, Denmark

⁵ Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

⁶ Department of Anaesthesiology, Zealand University Hospital, Køge, Denmark

⁷ Department of Anaesthesia and Intensive Care, Kolding Hospital, University of Southern Denmark, Kolding, Denmark

⁸ Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark

⁹ Department of Intensive Care, Rigshospitalet, Copenhagen, Denmark

Short title: Long-term outcomes in the HOT-ICU trial

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/AAS.13995](https://doi.org/10.1111/AAS.13995)

This article is protected by copyright. All rights reserved

Word count (excluded abstract and references): 2520

Corresponding author: Elena Crescioli, MD, Department of Anaesthesia and Intensive Care, Aalborg University Hospital, Hobrovej 18-22, 9100 Aalborg, Denmark, telephone: +45 97664372, fax: +45 97661996 e-mail: e.crescioli@rn.dk

Abstract

Background: Although supplemental oxygen can be lifesaving, liberal oxygen administration causing hyperoxaemia, may be harmful. The targets for oxygenation in patients with acute hypoxaemic respiratory failure acutely admitted to the intensive care unit (ICU) are strongly debated, and consensus on which targets to recommend has not been reached. The Handling Oxygenation Targets in the ICU (HOT-ICU) trial is 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. In this study, we aim to evaluate the effects of these targets on long-term cognitive and pulmonary function in Danish patients, enrolled in the HOT-ICU trial and surviving to one-year follow-up. 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: All patients enrolled in the HOT-ICU trial at Danish sites and surviving to one year after randomisation are eligible to participate. The last patient is expected to be included by November 2021. A Repeatable Battery for the Assessment of Neuropsychological Status and a body plethysmography, including diffusion capacity for carbon monoxide, both pre-planned secondary long-term outcomes of the HOT-ICU trial, will be obtained.

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

Introduction

Oxygen is one of the most commonly used medicines in critically ill adults.¹ Although it can be lifesaving, liberal oxygen administration leading to hyperoxaemia, may have harmful effects² – e.g. cellular damage mediated by reactive oxygen species.^{3,4} In the last decades, targeting oxygenation in critically ill patients admitted to the intensive care unit (ICU) with acute hypoxaemic respiratory failure has been strongly debated and agreement on recommended oxygenation targets has not been reached. The protocol for mechanical ventilation provided by the acute respiratory distress syndrome (ARDS) network⁵ has supported a low oxygenation target of a partial pressure of arterial oxygen (PaO₂) between 7.3 and 10.7 kPa or a peripheral saturation between 88% and 95%.^{6,7} While it has been considered the standard of care in ARDS patients, this oxygenation target has never been tested in clinical trials.^{6,7} Consequently, the evidence is sparse⁸ and clinical guidelines do not give recommendations on targeting oxygenation.^{9,10} Recently, several randomised clinical trials (RCTs), investigating lower versus higher oxygenation strategies in the ICU, have been published.¹¹⁻¹³ Neither of these provide clear evidence regarding optimal oxygenation targets when treating adult ICU patients in terms of effects on mortality.¹⁴

Many organs can remain impaired after discharge from the ICU leading to temporal or permanent dysfunctions.¹⁵ Long-term cognitive sequelae after ICU admissions have been described especially in mechanically ventilated patients with ARDS,¹⁶⁻¹⁹ and a lower PaO₂ has been associated with poorer cognitive performance.²⁰ Regarding long-term pulmonary function, most studies have been conducted in ARDS populations,²¹⁻²⁵ showing potential disadvantages with a higher oxygenation target.²⁶ However, the severity of the organ impairments has predominantly been mild and the association with oxygenation targets is difficult to quantify.¹⁵

The Handling Oxygenation Targets in the ICU (HOT-ICU) trial is the largest trial to date exploring lower versus higher oxygenation targets in adult patients acutely admitted to the ICU with hypoxaemic respiratory failure. The trial found no differences in the primary outcome being 90-day all-cause mortality, or in the secondary outcomes at 90 days (number of patients with serious adverse events, percentage of days alive without life-support in the ICU, and percentage of days alive and out of hospital).¹³ In the present study, we aim to evaluate the effects of the two oxygenation targets on cognitive and pulmonary functions in Danish patients, enrolled in the HOT-ICU trial and who survive to one year after randomisation. 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.

Methods

Study design

This is a protocol and statistical analysis plan for two pre-planned secondary long-term outcomes of the HOT-ICU trial, explored in a subgroup of survivors included at selected Danish ICUs. The last patient was included in the HOT-ICU trial on the 3rd of August 2020 and one-year follow-up is currently being conducted.

The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.²⁷ The SPIRIT 2013 checklist is presented in Appendix S1.

The Danish cohort of the HOT-ICU trial

The HOT-ICU trial is an investigator-initiated, pragmatic, multicentre, randomised, outcome-assessor blinded, parallel-group trial of a lower versus a higher oxygenation target in adult patients acutely admitted to the ICU with hypoxaemic respiratory failure, defined as a need of at least 10 litres of oxygen per minute in an open system or a fraction of inspired oxygen (FiO₂) of at least 0.50 in a closed system.¹³ Patients were randomised 1:1 within 12 hours after ICU admission to either a PaO₂ target of 8 kPa (lower target) or 12 kPa (higher target) up to a maximum of 90 days after randomisation. The HOT-ICU trial was performed in 35 ICUs in 7 countries and enrolment was completed in August 2020 with a total of 2928 patients included. The Danish trial cohort consists of 2332 patients.

Approvals and registrations

The trial was approved by the Danish Health and Medicines Agency (AAUH-ICU-01, EudraCT no. 2017-000632-34); the Committee on Health Research Ethics in the North Denmark Region (N-20170015); the Danish Data Protection Agency (2008-58-0028); and all required authorities in the participating countries, and prospectively registered at European clinical trials database (EudraCT number 2017-000632-34) and at ClinicalTrials.gov (Identifier: NCT03174002).^{13,28,29}

Additional details on the HOT-ICU trial are available in the primary publication and elsewhere.^{13,28,29}

Study population and one-year cognitive and pulmonary follow-up

All patients enrolled in the HOT-ICU trial at Danish sites and surviving until one year after randomisation are eligible to participate. The inclusion criteria are the following: 1) included in the HOT-ICU trial; 2) able to speak and understand the Danish language; 3) informed consent to participate in the long-term evaluations of cognitive and lung function. Patients will be excluded from the trial if they meet any of the following criteria: 1) more than 18 months since the inclusion in the HOT-ICU trial – this limit was

previously set to 15 months and later extended to 18 at the COVID-19 pandemic outbreak with consequent suspension of outpatient clinics' activities; 2) consent not obtainable according to national regulations; 3) body weight above 150 kg (only an exclusion criterion for the lung function test).

Setting

The cognitive evaluation and lung function tests are performed at selected Danish hospitals. The cognitive evaluation is performed by trained research personnel from Aalborg University Hospital, Kolding Hospital, and Zealand University Hospital Køge; the lung function tests are undertaken at the Departments of Pulmonology at Aalborg University Hospital, Kolding Hospital, and Herlev & Gentofte Hospital.

Enrolment

At one-year follow-up, all survivors included in the HOT-ICU trial are contacted by telephone for a health-related quality of life (HRQoL) interview within 1 months after the date of one-year follow-up. Eligible Danish patients are, at this point, invited to participate in the present study and enrolled after written informed consent is obtained. Inclusion and exclusion of patients will be reported according to the Consolidated Standards of Reporting Trials statement.³⁰

Outcome measures

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

- a) A global cognitive score obtained from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),³¹ 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; i.e. immediate memory; delayed memory; attention; language; and visuospatial/constructional abilities.
- b) A 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).³²

Exploratory outcomes include pulmonary plethysmography with measurements of dynamic and static lung function; a) forced expiratory volume in the first second (FEV₁), b) forced vital capacity (FVC), c) the ratio between FEV₁ and FVC (FEV₁/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. The RBANS scores in all separate five cognitive domains will be reported as well.

Blinding

HRQoL interviews are conducted by blinded interviewers, and consequently, recruitment to the current study is also blinded. Additionally, RBANS and pulmonary function tests are performed by blinded research staff personnel ensuring full outcome assessment blinding for the long-term outcomes. The trial statistician will as well be blinded for the trial allocations during all analyses.

Data management

No data from the patient files are collected. RBANS and lung function data will be stored in accordance with the Danish legislation and the trial is reported to The Danish Data Protection Agency. The data will be merged with the electronic HOT-ICU database.

Statistical analysis

Baseline variables

Baseline variables will be reported as numbers and percentages for categorical variables. Means and standard deviations (SDs) or medians with interquartile ranges (IQRs) will be reported for continuous variables, as appropriate.

Evaluation of sample representativeness

In order to evaluate whether our sample is representative of the entire trial population alive at one year, we will compare the baseline variables and non-mortality secondary outcomes of the HOT-ICU trial being the number of patients with serious adverse events in the ICU, percentage of days alive without life-support in the ICU in 90 days, percentage of days alive and out of hospital in 90 days, and EuroQol visual analogue scale score³³ from the HRQoL interviews at one-year follow-up between the subpopulation included in the present study and the remaining HOT-ICU trial cohort alive at one year from randomisation. We will use a chi-square test for categorical data and a parametric or non-parametric test for continuous data, as appropriate.

Pre-planned long-term outcomes

We will conduct all analyses according to the intention-to-treat principle unless specified otherwise.³⁴ The intention-to-treat population includes all randomised Danish patients surviving to one year after randomisation, except where follow-up data cannot be obtained due to withdrawal of consent according to national regulations.³⁵⁻³⁷

The pre-planned long-term outcomes will be compared between the intervention groups using a generalised linear model or a non-parametric test. Results will be presented as absolute differences with

multiplicity adjusted CIs. Adjustments of CIs due to multiple outcomes will be performed as according to the procedure specified by Jakobsen et al³⁸ and in the statistical analysis plan for the HOT-ICU trial.²⁹ With an adjusted CI of 98.75%. Adjusted P-values below 0.0125 will be considered definitely significant and P-values above 0.0125 will be considered definitely non-significant. P-values below 0.05 but above 0.0125 will be considered only possibly significant and thus not confirmative.

All generalised linear models will initially use normal distribution or alternatively Poisson distribution or negative binomial distribution,³⁹ and will be adjusted for the stratification variables site, known chronic obstructive pulmonary disease (COPD), and haematological malignancy.⁴⁰ If assumptions for these distribution are not met, we will analyse the data using the nonparametric Van Elteren test adjusting for site, only.⁴¹

Secondary analyses of the outcomes, using a generalised linear model will be performed, adjusting for stratification variables together with important prognostic baseline factors: age, active metastatic cancer, type of admission (medical, elective surgery, or emergency surgery) and Sequential Organ Failure Assessment Score. If assumptions for this analysis is not met, we will apply a general linear model for the mean regardless of any non-parametric data distributions to allow for the multiple adjustments required.

Exploratory outcomes

Each exploratory outcome will be compared between the intervention groups using a generalised linear model or a nonparametric test with adjustments for stratification variables (site, known COPD, haematological malignancy). Evaluations of significance will be based on the P-values from these regression analyses and the absolute risk differences with 95% CIs will be reported. No adjustments for multiplicity will be conducted for the explorative outcomes.

Power sample calculation

Assuming an RBANS mean global score \pm SD of 80 ± 20 ⁴² in the HOT-ICU control group and an RBANS global score of 75 ± 20 in the intervention group, 2 x 359 patients are required for confirmative results with $\alpha = 0.0125$ (two-sided) and $\beta = 0.2$ (i.e. a power of 80%). The predicted DLCO \pm SD at one-year follow-up in a small cohort of ARDS patients was $70\% \pm 20\%$.²¹ Assuming that this will also be the result in the HOT-ICU intervention group and with an expected higher value in the HOT-ICU control group being $75\% \pm 20\%$, 2 x 359 patients are also required for confirmative results in this outcome with $\alpha = 0.0125$ (two-sided) and $\beta = 0.2$ (i.e. power of 80%). Conversely, to obtain explorative results with a two-sided α of 0.05, 2x253 patients for both outcomes are required.

Discussion

This one-year follow-up study of the HOT-ICU trial 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 RCT, the Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy (ICU-ROX), has performed long-term follow-up with cognitive evaluation on survivors conducted at 180 days post-randomisation. The investigators tested a lower versus a higher oxygenation target in mechanically ventilated patients and found no significant between-group difference in cognitive impairment.⁴³ Otherwise, existing evidence comes from observational studies, primarily conducted in ARDS patients.¹⁶⁻²⁵

The strengths of our study are that the cognitive and pulmonary evaluations were pre-planned long-term outcomes,^{13,28,29} and that they are assessed by research staff strictly blinded to the intervention.

Moreover, both assessments are performed by trained personnel at three selected hospitals in Denmark to enhance the quality and to minimise variability, even if this could affect the number of participants due to geographical reasons. Additionally, the methodology of the present study has been prepared in agreement with the relevant statement according to the study design.²⁷ Also, the HOT-ICU trial's protocol²⁸ and statistical analysis plan²⁹ are predefined and were published prior to randomisation of the last patient. The present study has some limitations. Only survivors at selected Danish sites are invited to participate. However, the Danish subpopulation represents the vast majority of the trial with 2332 patients out of 2928 (79.6%) included from 19 of the 35 recruiting sites. Additionally, we expected a substantially lower 90-day all-cause mortality than what was found in the primary publication.¹³

Consequently, with an one-year mortality of around 42% fewer potential patients are being eligible than expected. Finally, the outbreak of the COVID-19 pandemic caused outpatient clinics to close and led to a significant loss of eligible patients, despite the inclusion period being increased from 15 to 18 months after randomisation upon the approval from the Ethics Committee. To evaluate the impact of the limitations of the trial, we will compare the baseline variables and non-mortality secondary outcomes of our subpopulation with the remaining HOT-ICU trial cohort alive at one-year post-randomisation.

In conclusion, we aim to evaluate the long-term effects of a higher versus a lower oxygenation target on both cognitive and pulmonary long-term function in a Danish subpopulation of the HOT-ICU trial. As both

outcomes are pre-planned, with emphasis on minimising risks of bias, the present study will provide important information on the long-term effects of targeted oxygen therapy in patients with acute hypoxaemic respiratory failure admitted to the ICU.

Status of the study

The study is currently recruiting. By 30th September 2021, we have enrolled 193 patients for the cognitive evaluation and 195 for the lung function test, respectively. The last patient is expected to be included by November 2021.

Acknowledgements

We thank all participating patients and relatives, and the participating clinical research staff at Aalborg University Hospital, Kolding Hospital, Zealand University Hospital Køge, and Herlev & Gentofte Hospital.

Funding

This study is funded by the Novo Nordisk Foundation (NNF18OC0034614) and Danish Ministry of Higher Education and Science (0238-00004B), who had no influence on study design, scientific content of the protocol, trial conduct, data collection or analysis, interpretation of the results, or on the final publication.

Conflict of interest

The authors have no conflicts of interest.

Publishing of results

All results of the study will be published regardless of the outcomes.

Authors' contributions

EC and BSR drafted the manuscript for this paper in close collaboration with TLK and OLS. Furthermore JØR, UMW, JUSJ, LMP, ACB, TL and AP all made substantial contributions to the manuscript and provided important scientific input. All authors read and approved the final version of the paper.

References

1. Koehler N, Goubeaud M, Hildebrandt O, Sohrabi AK, Koehler U. [The history of oxygen--from its discovery to its implementation as medical therapy]. *Pneumologie*. 2011;65(12):736-741.
2. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care*. 2015;5(1):42-42.
3. 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(1):284.
4. Chow CW, Herrera Abreu MT, Suzuki T, Downey GP. Oxidative stress and acute lung injury. *Am J Respir Cell Mol Biol*. 2003;29(4):427-431.
5. Thompson BT, Bernard GR. ARDS Network (NHLBI) studies: successes and challenges in ARDS clinical research. *Crit Care Clin*. 2011;27(3):459-468.
6. 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(4):327-336.
7. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
8. Kallet RH, Branson RD. Respiratory controversies in the critical care setting. Do the NIH ARDS Clinical Trials Network PEEP/FIO2 tables provide the best evidence-based guide to balancing PEEP and FIO2 settings in adults? *Respir Care*. 2007;52(4):461-475; discussion 475-467.
9. 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(3):286-297.
10. 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(9):1253-1263.
11. Barbateskovic M, Schjørring OL, Russo Krauss S, et al. Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. *Cochrane Database Syst Rev*. 2019;2019(11).
12. Barrot L, Asfar P, Mauny F, et al. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *N Engl J Med*. 2020;382(11):999-1008.

- Accepted Article
13. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. *N Engl J Med.* 2021;384(14):1301-1311.
 14. Barbateskovic M, Schjørring OL, Krauss SR, et al. Higher vs Lower Oxygenation Strategies in Acutely Ill Adults: A Systematic Review With Meta-Analysis and Trial Sequential Analysis. *Chest.* 2020.
 15. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Crit Care Med.* 2011;39(2):371-379.
 16. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson LV. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;160(1):50-56.
 17. Rothenhäusler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry.* 2001;23(2):90-96.
 18. Hopkins RO, Weaver LK, Chan KJ, Orme JF, Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc.* 2004;10(7):1005-1017.
 19. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF, Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2005;171(4):340-347.
 20. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med.* 2012;185(12):1307-1315.
 21. Herridge MS, Tansey CM, Matté A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. *N Engl J Med.* 2011;364(14):1293-1304.
 22. Schelling G, Stoll C, Vogelmeier C, et al. Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Med.* 2000;26(9):1304-1311.
 23. Neff TA, Stocker R, Frey HR, Stein S, Russi EW. Long-term assessment of lung function in survivors of severe ARDS. *Chest.* 2003;123(3):845-853.
 24. Orme J, Jr., Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2003;167(5):690-694.
 25. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348(8):683-693.

26. 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(4):613-618.
27. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207.
28. 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(7):956-965.
29. Schjørring OL, Klitgaard TL, Perner A, et al. The handling oxygenation targets in the intensive care unit (HOT-ICU) trial: Detailed statistical analysis plan. *Acta Anaesthesiol Scand*. 2020;64(6):847-856.
30. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8:18.
31. 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(3):310-319.
32. C DRB, JM BH. Lung Diffusing Capacities (D(L)) for Nitric Oxide (NO) and Carbon Monoxide (CO): The Evolving Story. *Compr Physiol*. 2019;10(1):73-97.
33. 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(10):1727-1736.
34. DeMets DL, Cook T. Challenges of Non-Intention-to-Treat Analyses. *Jama*. 2019;321(2):145-146.
35. International conference on harmonisation; guidance on statistical principles for clinical trials; availability--FDA. Notice. *Fed Regist*. 1998;63(179):49583-49598.
36. Gabriel SE, Normand SL. Getting the methods right--the foundation of patient-centered outcomes research. *N Engl J Med*. 2012;367(9):787-790.
37. Schmiemann G. [The preliminary draft of the methodology report by the Patient-Centered Outcomes Research Institute]. *Z Evid Fortbild Qual Gesundheitswes*. 2012;106(7):496-499.
38. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Med Res Methodol*. 2014;14:120.
39. Andersen PK SL. Statistics for Biology and Health: Regression with Linear Predictors. 2010.

- Accepted Article
40. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *Bmj*. 2012;345:e5840.
 41. Jakobsen J, Tamborrino M, Winkel P, et al. Count Data Analysis in Randomised Clinical Trials. *Journal of Biometrics & Biostatistics*. 2015;6:227.
 42. Pandharipande PP, Girard TD, Ely EW. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2014;370(2):185-186.
 43. Mackle D, Bellomo R, Bailey M, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med*. 2020;382(11):989-998.