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ORIGINAL ARTICLE

The handling oxygenation targets in the intensive care unit (HOT-ICU) trial: Detailed statistical analysis plan

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Background: No solid evidence exists on optimal oxygenation targets in intensive care patients. The handling oxygenation targets in the intensive care unit (HOT-ICU) trial assesses the effects of a targeted arterial oxygen tension of 8 vs 12 kPa on 90-day mortality in acutely admitted adult patients with hypoxaemic respiratory failure. This article describes the detailed statistical analysis plan for the predefined outcomes and supplementary analyses in the HOT-ICU trial.

Methods: The trial will include 2928 patients to be able to detect or reject a true 20% relative risk reduction in the primary outcome of 90-day all-cause mortality with an α of 5% and a β of 10%. Analyses of the primary and secondary outcomes will be conducted according to the intention-to-treat principle and adjusted for stratification variables. The primary outcome and dichotomous secondary outcomes will be analysed using a generalised linear model with a log-link and binomial error distribution. For the primary outcome, a 95% confidence interval (CI) not including 1.00 for the risk ratio will be considered statistically significant. Continuous secondary outcomes will be analysed using a generalised linear model or nonparametric test. CIs adjusted

for the multiple secondary outcomes not including the null effect will be considered statistically significant. One planned interim analysis has been conducted.

Conclusions: The HOT-ICU trial and the pre-planned statistical analyses are designed to minimise bias and produce high quality data on the effects of a lower vs a higher oxygenation target throughout ICU admission in acutely admitted adult patients with hypoxaemic respiratory failure.

Registration: ClinicalTrials.gov identifier: NCT03174002, date of registration: June 2, 2017. European clinical trials database, EudraCT number 2017-000632-34.

1 | INTRODUCTION

The oxygenation levels in patients admitted to intensive care units (ICUs) worldwide differ extensively.[1-7] Several randomised clinical trials investigating the effects of a higher vs a lower oxygenation strategy for patients admitted to the ICU have been published throughout the last 5 years,[8-11] the results, however, remain inconclusive.[11,12] We present a detailed statistical analysis plan of the to date largest and still ongoing randomised clinical trial of higher vs lower oxygenation targets in the ICU, the handling oxygenation targets in the intensive care unit (HOT-ICU) trial. The HOT-ICU trial randomises acutely admitted adult ICU patients with hypoxaemic respiratory failure to an arterial oxygen tension (PaO_2) target of 8 kPa (intervention) vs a PaO_2 target of 12 kPa (control) throughout the duration of ICU admission, including readmissions, up until 90 days after randomisation. The trial is prospectively registered at ClinicalTrials.org (NCT03174002) and the protocol has been published.[13] The current protocol is version 2.1 of 14 August 2019 (www.cric.nu/hot-icu).

2 | METHODS

This detailed statistical analysis plan represents the complete overview of the statistical methods which will be used for analysing all outcomes in the HOT-ICU trial. The plan is prepared before the last patient is randomised in the HOT-ICU trial, and before the database is closed and the data analysis commenced. The Steering Committee of the HOT-ICU trial approved this analysis plan on 12 February 2020. All analyses of the primary and secondary outcomes of the HOT-ICU trial will be conducted according to this publication and according to the previously published trial protocol.[13]

The HOT-ICU trial has been approved by the Danish Health and Medicine Agency (AAUH-ICU-01), the Committee on Health Research Ethics in the North Denmark Region (N-20170015), the Danish Data Protection Agency (2008-58-0028) and by all required authorities in participating countries.

3 | OUTCOME MEASURES

The primary outcome measure is all-cause mortality within 90 days after randomisation.

The secondary outcomes are (a) number of patients with one or more serious adverse events (SAEs) defined as new myocardial ischaemia, new ischaemic stroke, new intestinal ischaemia or a new episode of shock in the ICU within 90 days after randomisation (patients transferred to an ICU not participating in the HOT-ICU trial will be considered discharged from the ICU); (b) days alive without life support (the use of renal replacement therapy, vasopressor/inotrope support or respiratory support defined as noninvasive ventilation (NIV), non-intermittent continuous positive airway pressure (CPAP) or invasive mechanical ventilation) in the 90-day period; (c) days alive and out of hospital in the 90-day period; (d) all-cause mortality one year after randomisation; (e) health-related quality of life (HRQoL) assessed using EuroQol 5 dimensions, five-level questionnaire and EQ visual analogue scale (EQ-5D-5L)[14] scores 1 year after randomisation; (f) repeatable battery for the assessment of neuropsychological status (RBANS)[15] 1 year after randomisation at selected sites; (g) pulmonary function 1 year after randomisation at selected sites (a post hoc planned secondary outcome); and (h) a health economic analysis.

A new episode of shock is defined as p-lactate >2.0 mmol/L and the use of continuous vasopressor or inotropic treatment on any day in the ICU in participants who did not have shock at baseline (p-lactate ≤2.0 mmol/L or no use of continuous vasopressor or inotropic treatment) or were shock free on any of the foregoing post-randomisation days. Shock free in any day is defined as highest daily p-lactate ≤2.0 mmol/L and no use of vasopressor or inotropic treatment.

The HRQoL, EQ-5D-5L scores will be analysed with the EQ visual analogue scale score being the primary HRQoL outcome. The scores from each of the five EQ-5D-5L dimensions will be reported as supplementary outcomes.[14]

The RBANS cognitive function test will be reported with the overall global cognition score as the primary cognitive outcome.[15]

In the pulmonary function tests, the carbon monoxide diffusion capacity (DLCO) will be reported as the primary pulmonary outcome.

All other outcomes are defined as their respective daily registered variables as presented in Table 2.

4 | BLINDING

The allocated oxygenation targets will not be blinded to clinicians, patients, or relatives. Outcome assessments will be blinded as

previously described.[13] The trial statistician will be blinded and will receive a data file with the oxygenation targets randomly marked X or Y, or similarly. The blinded allocated oxygenation targets (X and Y) in the cumulated results will be attached to the final data set by an unblinded data manager, who is not involved in the trial conduct and is not a member of the Steering Committee, prior to sending it to the trial statistician. Thus, the Steering Committee will be blinded to the oxygenation targets in the cumulated data, and in the results of the statistical analyses. The primary abstract will be drafted in two versions, one where X represents the PaO_2 oxygenation target of 8 kPa and one where it represents the PaO_2 oxygenation target of 12 kPa, before the data are unblinded.

The data monitoring and safety committee (DMSC) will remain blinded unless unblinding is specifically requested as previously described.[13]

5 | SAMPLE SIZE AND POWER ESTIMATIONS

The sample size of 2928 patients has been calculated based on the primary outcome of 90-day mortality, with a maximal type 1 error of 5% and a power of 90% to detect or reject a true 20% relative risk reduction in the estimated control group mortality of 25%, as previously described.[13] For the secondary outcomes, this sample size will give a power of 80% to detect or reject an increase in the proportion of patients with one or more SAEs from 9% to 12% (a 33% relative risk increase) or a decrease from 9% to 6.3% (a 30% relative risk reduction); a power of 80% to detect or reject an absolute difference of 5 percentage points in mean percentage of days, calculated as the number of days alive without the use of life support divided by the number of days alive during the 90-day period; a power of 80% to detect or reject an absolute difference of 5 percentage points in days alive and out of hospital in the 90-day period; and a power of 80% to detect or reject a reduction in 1-year mortality from 30.0% to 25.4% (a 15.3% relative risk reduction) or an increase in 1-year mortality from 30.0% to 34.8% (a 16.0% relative risk increase) assuming an absolute increase in mortality from 90 to 365 days of 5 percentage points, and a 90-day mortality of 25% in the control group. The estimated prevalences of the secondary outcomes in the control group are based on the results of two previously conducted trials in our research collaboration.[16,17] For the EQ-5D-5L outcome, we do not have sufficient knowledge of the distribution of the outcomes in the control population or of the expected effect of the intervention, and furthermore, the distribution of this outcome will likely be skewed due to non-survivors receiving the worst possible scores. Therefore, no realistic power estimations can be conducted for this outcome, and so we refrain from such calculations to avoid presenting a false impression of precision.

6 | REGISTERED VARIABLES

The registered variables at baseline, daily during ICU admission, and at 90-day and 1-year follow-up are presented in Tables 1-3, respectively. Complete follow-up of any life support used in the 90-day period in patients transferred to a non-participating ICU will be sought obtained through mail or telephone contact.

7 | GENERAL ANALYTICAL PRINCIPLES

We will conduct all analyses according to the intention-to-treat principle unless stated otherwise.[18] The intention-to-treat population includes all randomised patients except those where follow-up data cannot be obtained due to withdrawal of consent according to national regulations.[19-21] A 95% confidence interval (CI) not including 1.00 for the risk ratio will be considered statistically significant. Significance tests will be two sided, a *P*-value below .05 is considered statistically significant unless specified otherwise. CIs adjusted for the multiple secondary outcomes not including the null effect will be considered statistically significant. When assessing the results, we will adopt the five-step procedure as described by Jakobsen et al,[22] including reporting of CIs and exact *P*-values, adjustment for multiple testing, adjustment in case of premature trial termination, reporting of a Bayes factor, and assessment of the clinical relevance of the results.

8 | TRIAL PROFILE

The flow of patients will be depicted using the consolidated standard of reporting trials (CONSORT) diagram,[23] presenting the number of patients assessed for eligibility, that is, patients fulfilling all inclusion criteria,[13] the number of excluded patients with reasons for exclusion, and the number of patients included in the final analyses.

9 | MISSING DATA

If less than 5% of the data are missing in any primary or secondary outcome analysis, a complete case analysis without imputation of missing values will be performed. If missing data exceed 5%, a blinded statistician will assess whether data are 'missing completely at random' based on a rational assessment of the pattern of missing data.[24] Little's test will be used if doubt remains.[25] If the data are judged missing at random, but not 'completely at random', multiple imputation using chained equations will be performed by creating at least 10 imputed data sets.[26,27] In any multiple imputation conducted, we will use all relevant outcomes, all stratification variables and the following baseline characteristics: age, gender, height, ICU admission type, respiratory status, PaO_2/fraction of inspired oxygen (FiO_2) ratio, shock, acute illnesses, chronic comorbidities and the Sequential Organ Failure Assessment (SOFA) score.[28] If multiple imputation is used, then the primary result of the trial will be based on the imputed data. The analysis of the non-imputed data set will also be made available. Also, if multiple

TABLE 1 Baseline registrations

Registration	Definition
Age	Calculated from birth year
Gender	Genotypic
Height	If bilaterally amputated, estimate original height
Hospital admission	Date
ICU admission	Date and time. If transferred from another ICU, the primary ICU admission time is registered
Surgery (y/n)	'Yes' if admission was directly from the operating or recovery room after surgery
Surgery type[a]	Acute or elective
Respiratory status[b]	
Respiratory support (y/n)	NIV, mask CPAP or invasive mechanical ventilation
Support type[a]	Invasive or noninvasive
EPAP or CPAP[c]	Last setting before randomisation
TV[d]	Last representative measure before randomisation
P_{peak}[d]	Last representative measure before randomisation
PEEP[d]	Last setting before randomisation
PaO_2	Last ABG before randomisation
SaO_2	Last ABG before randomisation
p-lactate	Last ABG before randomisation
FiO_2[e]	At the time of the last ABG before randomisation
Acute illness[f]	
Pneumonia (y/n)	As defined by clinicians and noted in the patient files
Multiple trauma (y/n)	Acute accident with lesions in two anatomical sites or more
Stroke (haemorrhagic or ischaemic) (y/n)	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 CT or MRI scan
Myocardial infarction (y/n)	Verified by ECG changes, significant rise in coronary biomarkers and/or acute PCI or CABG conducted
Cardiac arrest (y/n)	Clinically diagnosed with initiated cardiopulmonary resuscitation, leading to or occurred during current ICU admission
Intestinal ischaemia (y/n)	Verified by surgery, gastroscopy, colonoscopy, or CT or MRI angiography
ARDS (y/n)	According to the Berlin definition,[39] judged by clinicians
Chronic co-morbidity	
Active haematological malignancy[g] (y/n)	Defined from the WHO 2017 classification,[40] is considered active if the diagnosis resulted in any interventions conducted within the last 6 mo prior to randomisation
COPD[g] (y/n)	Defined as previous spirometry in stable phase diagnostic of COPD,[41] or COPD in the anamnesis and daily use of inhaled β_2-adrenergic bronchodilators, anticholinergic bronchodilators or glucocorticoids
Ischaemic heart disease (y/n)	Previous myocardial infarction, previously conducted PCI or CABG, or previous stable or unstable angina pectoris or use of nitrates indicating this
Chronic heart failure (y/n)	Chronic LVEF ≤40% or diagnosed chronic heart failure with preserved LVEF
Active metastatic cancer (y/n)	Any metastasis from a malignant non-haematological neoplasm, which was not considered eradicated at randomisation
Chronic dialysis (y/n)	Any RRT on a regular basis prior to hospital admission including haemodialysis and peritoneal dialysis
Habitual creatinine >110 mol/L[h] (y/n)	Known or estimated
SOFA score[i] [28]	
GCS[42]	Lowest score, if actively sedated the estimated last score prior to sedation will be registered
MAP	Lowest measurement

(Continues)

TABLE 1 (Continued)

Registration	Definition
Use of inotropes or vasopressor	As defined in the SOFA score[28]
Bilirubin	Highest value measured
Platelets	Lowest value measured
Creatinine	Highest value measured
24-h urinary output	Estimated to be <200 mL, 200-500 mL or >500 mL if no precise value is available

Abbreviations: ABG, arterial blood gas analysis; ARDS, acute respiratory distress syndrome; 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 scale; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NIV, noninvasive ventilation; PaO_2, arterial oxygen tension; PCI, percutaneous coronary intervention; PEEP, positive end-expiratory pressure; P_{peak}, peak inspiratory pressure; RRT, renal replacement therapy; SaO_2, arterial oxygen saturation; SOFA, sequential organ failure assessment; TV, tidal volume.

[a]Only registered if 'yes' to previous question.

[b]At randomisation.

[c]Only registered if 'noninvasive' respiratory support.

[d]Only registered if 'invasive' respiratory support.

[e]In open systems, the FiO_2 will be calculated from standardised FiO_2 tables (see Appendix S1).

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

[g]Stratification variables.

[h]Only registered if 'no' to previous question.

[i]From the last 24 h prior to randomisation except respiratory system status, which will be defined as use of respiratory support (NIV, mask CPAP or invasive mechanical ventilation) at randomisation, and the PaO_2/FiO_2 ratio used will be from the last ABG sample prior to randomisation.

imputation is used, we will in addition provide a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missing data. In the best-worst case scenario, it is assumed that patients lost to follow-up in the experimental group have had a beneficial outcome (eg. have survived, had no SAEs etc) and those with missing outcomes in the control group have had a harmful outcome (eg. have not survived, have had SAEs etc). Conversely, in the worst-best case scenario, it is assumed that patients who were lost to follow-up in the experimental group have had a harmful outcome and that those lost to follow-up in the control group have had a beneficial outcome. For continuous outcomes, a beneficial outcome will be defined as the group mean plus two standard deviations (SDs) and a harmful outcome will be defined as the group mean minus two SDs.

10 | STATISTICAL ANALYSES

10.1 | Primary outcome

The primary outcome of 90-day mortality will be compared between the intervention groups using a generalised linear model with a log-link and binomial error distribution with adjustment for stratification variables (site, known chronic obstructive pulmonary disease (COPD) and active haematological malignancy).[29] Evaluation of significance will be based on the p-value from this regression analysis and the absolute difference and risk ratio with 95% CIs will be reported. The time to death will be illustrated with Kaplan-Meier plots. Cox proportional hazards models with adjustments for stratification variables will be conducted as supplementary analyses. The Bayes factor[30] for the primary outcome will be reported; the prior alternative hypothesis to be used in the calculations of the Bayes factor will be the expected intervention effect of a 20% relative risk reduction used in the sample size estimation. A secondary analysis will be conducted with adjustments for stratification variables as well as for important prognostic baseline factors being age, active metastatic cancer, type of admission (medical, elective surgical or emergency surgical) and the SOFA score.

Sensitivity analyses of the primary outcome measure will be conducted in specified per-protocol populations as previously described[13] with the primary sensitivity analysis being all randomised patients, except patients with a major protocol violation (MPV)[13] in two or more consecutive 12-hour intervals, corresponding to the patient being at least 24 hours off target; only consecutive MPVs that deviate to the same side (either above or below the allocated oxygenation target) will exclude the participant.

10.2 | Secondary outcomes

The dichotomous secondary endpoints, that is, one or more SAEs during ICU admission, and all-cause mortality 1 year after randomisation, will be compared using a generalised linear model with a log-link and binomial error distribution with adjustment for stratification variables (site, known COPD and active haematological malignancy). Results will be presented as absolute differences and risk ratios with multiplicity adjusted CIs as specified below. The crude 1-year mortality will be illustrated with a Kaplan-Meier plot. The continuous

TABLE 2 Daily registrations during ICU admission

Registration	Definition
12-hour highest PaO_2	From 06:00 to 18:00 and from 18:00 to 06:00 respectively
Corresponding SaO_2 values	In the ABGs with the highest PaO_2
Corresponding FiO_2 levels[a]	At the time of the ABGs with the highest PaO_2
12-hour lowest PaO_2	From 06:00 to 18:00 and from 18:00 to 06:00 respectively
Corresponding SaO_2	In the ABGs with the lowest PaO_2
Corresponding FiO_2 levels[a]	At the time of the ABGs with the lowest PaO_2
Cumulated number of ABG samplings	For 24 h
Highest arterial p-lactate	For 24 h, if no arterial p-lactate is available, the highest venous p-lactate is registered
Continuous infusion of vasopressors or inotropes (y/n)	Includes dopamine, norepinephrine, epinephrine, phenylephrine, vasopressin, dobutamine, milrinone and levosimendan
RRT (y/n)	Any continuous or intermittent RRT. Days between any intermittently used RRT counts as 'yes'
Cumulated number of units of red blood cells transfused	For 24 h (the site average volume of red blood cell units is registered separately)
Respiratory support (y/n)	Any use of NIV, continuous mask CPAP or invasive mechanical ventilation. Intermittent CPAP does not count as respiratory support
Mechanical ventilation in prone position[b] (y/n)	Any proning of the patient due to hypoxic respiratory failure
Inhaled vasodilators[b] (y/n)	Use of inhaled nitric oxide or inhaled epoprostenol
ECMO[b] (y/n)	Any veno-venous, veno-arterial or arterio-venous ECMO used
Respiratory support type at 08:00[b]	Invasive or noninvasive, if any
EPAP or CPAP[c]	Representative setting closest to 08:00
TV[d]	Representative measure closest to 08:00
Ppeak[d]	Representative measure closest to 08:00
PEEP[d]	Representative setting closest to 08:00
Ischaemic SAEs	
New myocardial ischaemia (y/n)	ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or unstable angina pectoris according to the criteria of the clinical condition in question (eg. elevated biomarkers, ischaemic signs on ECG and clinical presentation), and receiving treatment as a consequence of this (reperfusion strategies, or initiation of or increased antithrombotic treatment)
New ischaemic stroke (y/n)	Cerebral CT or MRI scan conducted on this day with signs of new ischaemic stroke. Radiographic signs of old infarctions estimated to have occurred before randomisation is not considered new ischaemic stroke. Radiographically diagnosed diffuse anoxic brain injury after pre-randomisation cardiac arrest is not considered new ischaemic stroke
New intestinal ischaemia (y/n)	Onset of gastric, mesenteric or colonic ischaemia on this day, verified by exploratory or diagnostic abdominal surgery, endoscopic procedures or on CT or MRI angiography
Relation of the ischaemic SAE to the allocated oxygenation target[e]	Clinical evaluation by local investigator, answered: 'Yes, related', 'Possibly related', or 'No, not related'

Note: Daily variables are registered from 06:00 to 06:00 while admitted to the ICU for up to 90 d, starting at the time of randomisation and including readmissions.

Abbreviations: ABG, arterial blood gas analysis; CPAP, continuous positive airway pressure; CT, computed tomography; ECG, electrocardiography; ECMO, extracorporeal membrane oxygenation; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; MRI, magnetic resonance imaging; NIV, noninvasive ventilation; PaO_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; P_{peak}, peak inspiratory pressure; RRT, renal replacement therapy; SAE, serious adverse event; SaO_2, arterial oxygen saturation; TV, tidal volume.

[a]In open systems, the FiO_2 will be calculated from standardised FiO_2 tables (see Appendix S1).

[b]Only registered if 'yes' to 'respiratory support'.

[c]Only registered if 'noninvasive' respiratory support at 08:00.

[d]Only registered if 'invasive' respiratory support at 08:00.

[e]Only registered if 'yes' to any of the specified ischaemic SAEs, a required safety measure.

secondary outcomes of days alive without life support in the 90-day period, days alive and out of hospital in the 90-day period and the EQ visual analogue scale score of the EQ-5D-5L at 1-year follow-up will be analysed using a generalised linear model or a nonparametric test, adjusted for the stratification variables. Non-survivors will be assigned the lowest possible EQ visual analogue scale score of 0. In all secondary outcomes, except 1-year mortality, adjustments of the CIs due to multiple outcomes will be performed as according to the procedure specified by Jakobsen et al;[31] with seven secondary outcomes, to preserve a family wise error rate below 5%, the adjusted *P*-values for the secondary outcomes will be below .0125, equivalent of an adjusted CI of 98.75%. Thus, if the adjusted 98.75% CIs for the multiple secondary outcomes, except for 1-year mortality, does not include the null effect, the results will be considered statistically significant. Adjusted *P*-values below .0125 will be considered definitely significant and *P*-values above .0125 will be considered definitely non-significant. *P*-values below .05 but above .0125 will be considered only possibly significant and thus not confirmative. In

TABLE 3 Registrations available at 90-day and at 1-year follow-up

Registration	Definition
At 90-day follow-up	
ICU discharge[a]	Date and time, if any
Location after ICU discharge[b]	Discharge to 'General ward', 'ICU participating in HOT-ICU trial', 'ICU not participating in HOT-ICU trial', 'home (including nursing home or similar)' or 'Dead' (if the patient died during ICU admission)
Discharge from hospital[c] (y/n)	Within 90 d from randomisation
Date of hospital discharge[d]	
Readmission to hospital[d] (y/n)	Within 90 d from randomisation
Days in hospital during readmissions[e]	The number of calendar days, on which the patient was readmitted to the hospital within 90 d from randomisation, including the day/days of readmission and of any secondary hospital discharge/discharges but not including the primary admission
RRT outside the ICU[d] (y/n)	Any RRT used
Date of last RRT outside the ICU[f]	If intermittent RRT in ongoing at 90 d, this will be registered
Dead (y/n)	Death by any cause within 90 d from randomisation
Date of death[g]	
At 1-year follow-up	
Dead (y/n)	Death by any cause within 1 y from randomisation
EuroQol 5 dimensions 5 level questionnaire and EQ visual analogue scale scores[14]	Interviews with survivors will be conducted within 30 d from the 1-year follow-up date through blinded telephone interviews or in selected sites through self-complete paper questionnaires
Date of EuroQol obtainment	
By proxy EuroQol obtainment (y/n)	'Yes' if EuroQol data are obtained by proxy through relative or caregiver (by proxy obtainment is only allowed if the patients are incapable answering themselves)
RBANS[h] [15]	Face-to-face interview, conducted within 90 d from the 1-year follow-up date
Pulmonary function tests[h]	Whole-body plethysmography and DLCO, conducted within 90 d from the 1-year follow-up date

Abbreviations: DLCO, carbon monoxide diffusion capacity; HOT-ICU, handling oxygenation targets in the intensive care unit; ICU, intensive care unit; RBANS, the repeatable battery for the assessment of neuropsychological status; RRT, renal replacement therapy.

[a]Registered for every ICU admission.

[b]Available for every ICU discharge.

[c]Only registered if 'yes' to 'ICU discharge'.

[d]Only registered in 'yes' to 'discharge from hospital'.

[e]Only registered if 'yes' to 'readmission to hospital'

[f]Only registered if 'yes' to 'RRT outside the ICU'.

[g]Only registered if 'yes' to 'dead'.

[h]In survivors at selected sites only.

the secondary outcome of 1-year mortality, the CI of 95% will be retained, as this outcome is highly dependent on the primary outcome of 90-day mortality justifying the use of the unadjusted CI.

Supplementary analyses of one or more of the separate SAEs during ICU stay from the composite SAE endpoint will be conducted using a generalised linear model with a log-link and binomial error distribution with adjustment for stratification variables, and will be reported as exploratory results. The composite endpoint of days without life support will be reported for each of the individual components, that is, days alive without respiratory support, renal replacement therapy or circulatory support, respectively, as supplementary analyses. These data will be compared using a generalised linear model or a nonparametric test, adjusted for the stratification variables and will be reported as explorative results. Supplementary analyses of EQ-5D-5L scores from level 1 (best) to level 5 (worst) in each of the five dimensions will be compared using a generalised linear model or a nonparametric test, with adjustment for stratification variables, and will be reported as exploratory results. Non-survivors will be assigned the worst possible score of 5 in all EQ-5D-5L dimensions. Secondary supplementary analyses of the EQ visual analogue scale score and of scores in each of the five EQ-5L-5L dimensions will be conducted, in which non-survivors are omitted. All exploratory results will be reported with 95% CIs.

All generalised linear models of the secondary endpoints will initially use Poisson distribution or alternatively negative binomial distribution.[32] If assumptions for these distributions are not met, we will analyse the data using the nonparametric Van Elteren test adjusted for site, only.[33]

Full detailed analysis plans of the two secondary outcomes of RBANS and pulmonary function tests at 1-year follow-up, and of the health economic analysis, will be provided in separate publications.

10.3 | Subgroup analyses

As previously described,[13] we will conduct the following five pre-planned subgroup analyses, assessing the heterogeneity of intervention effects of the primary outcome: (a) in patients with shock at randomisation (yes/no), we hypothesise a greater reduction of the 90-day mortality in the 8 kPa PaO_2 target group in patients with shock; (b) in patients receiving invasive mechanical ventilation at randomisation (yes/no), we hypothesise a greater reduction of the 90-day mortality in the 8 kPa PaO_2 target group in invasively mechanically ventilated patients; (c) according to type of ICU admission (medical/elective surgical/emergency surgical), we hypothesise a successively greater reduction of the 90-day mortality in the 8 kPa PaO_2 target group in elective surgical, medical and acute surgical admissions, respectively; (d) in patients with known COPD at randomisation (yes/no), we hypothesise a greater reduction of the 90-day mortality in the 8 kPa PaO_2 target group in patients with known COPD; and (e) in patients with acute traumatic brain injury at randomisation (yes/no), we hypothesise a greater reduction of the 90-day mortality in the 8 kPa PaO_2 target group in patients with traumatic brain injury. Specifications on the post hoc defined subgroup analyses[13] will be supplied in separate publications. Subgroup comparisons will be conducted using a generalised linear model with a log-link and binomial error distribution with adjustment for stratification variables. We will apply tests of interaction for all subgroups in the regression analyses. Only the primary outcome will be evaluated in the subgroup analyses and no adjustments for multiplicity will be conducted.

10.4 | Baseline variables

Baseline variables will be reported as numbers and percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. As according to the CONSORT 2010 statement,[23] group differences in baseline variables will not be compared using significance testing unless specifically requested by peer reviewers.

10.5 | Intervention group separation

The oxygenation levels obtained in the intervention groups will be evaluated by reporting the patient median 12-hour highest and lowest PaO_2, respectively, during ICU admission up to a maximum of 90 days after randomisation. The patient median arterial oxygen saturation (SaO_2) and FiO_2 corresponding to the 12-hour highest and lowest PaO_2, respectively, will be reported similarly.

Supplementary graphs of the highest and lowest PaO_2 and corresponding SaO_2 and FiO_2 levels over the duration of the ICU admission will be presented.

To further characterise the actual oxygenation levels achieved, a pre-planned supplementary analysis, including all arterial blood gas (ABG) analyses conducted during ICU admission in the 90-day period from the subset of sites, from which full ABG data can be obtained, will investigate the time-weighted average (TWA) PaO_2. Further process variables include TWA SaO_2 and TWA FiO_2.

10.6 | ICU treatment

We will report the following data as the number and percentages for categorical variables and means with SDs or medians with IQRs for continuous variables, as appropriate, on the co-interventions conducted in the ICU according to the intervention groups: proportion of patients receiving invasive mechanical ventilation; proportion of patients receiving NIV or continuous mask CPAP; proportion of patients mechanically ventilated in prone position; proportion of patients receiving inhaled epoprostenol or nitric oxide; proportions of patients receiving extracorporeal membrane oxygenation; the patients' median daily number of ABG samplings; proportions of patients receiving vasopressors or inotropes; proportion of patients receiving renal replacement therapy; proportions of patients receiving red blood cell transfusion, and for patients receiving red blood cell transfusion, the patients' cumulated volume of red blood cells transfused. Additionally, for patients receiving invasive mechanical ventilation at 08:00, we will report the patients' median positive end-expiratory pressure (PEEP) at 08.00; the patients' median tidal volume (TV) in mL/kg predicted body weight (males: 50 + 0.91 [height−152.4 cm] and females: 45.5 + 0.91 [height−152.4 cm][34]) at 8:00; and the patients' median peak inspiratory pressure (P_{peak}) at 08:00. For patients receiving non-invasive ventilation or CPAP at 08:00, we will report the patients' median expiratory airway pressure or CPAP at 08.00.

10.7 | Interim analysis

The independent DMSC has performed a blinded pre-planned interim analysis after 90-day follow-up of 1464 patients equal to 50% of the sample size, evaluating the primary outcome of 90-day all-cause mortality and the secondary outcome of number of patients with one or more SAEs in the ICU,[13] and recommended to continue the trial.

11 | DISCUSSION

The optimal oxygenation targets in patients admitted to the ICU are currently unknown. The HOT-ICU trial, being the largest randomised clinical trial on the subject to date, will add important evidence to this area. This statistical analysis plan and the main protocol[13] have been conducted according to current recommendations.[35] The statistical analysis plan is available before randomisation of the last patient and importantly, before data analyses

are initiated. The analytical methods are selected to minimise the overall risk of bias. All planned analyses are meticulously described, and any changes made in the conducted analyses will be clearly marked as post hoc analyses in any publications, ensuring that these will be interpreted only as exploratory. We will employ adjustments for multiple outcomes in secondary outcomes, as recommended,[36] ensuring that these outcomes, along with the primary outcome, can be considered confirmatory.[37] Sample size calculations were based on the best available evidence of the mortality within the cohort at the time of designing the trial, and the targeted power of 90% should ensure an adequate sample size to show any clinically relevant effect of the intervention on the primary outcome. To ensure the best available estimate on the effects of higher vs lower oxygenation targets, we conducted, and reported in the protocol, a preliminary systematic review with meta-analysis and trial sequential analysis prior to designing the trial with updated and final results published in 2019.[12] Additionally, to ensure that the oxygenation target of the control group matched clinical practice, we conducted a preliminary observational cohort study in the Danish region of the sponsor site, confirming this. The results of the final extended cohort of this observational study, including only mechanically ventilated patients, were published in 2020.[38]

12 | DISSEMINATION

The primary outcome of 90-day mortality and the secondary outcomes of number of patients with one or more SAEs, days alive without life support in the 90-day period, and days alive and out of hospital in the 90-day period will be included in the primary publication submitted to a peer-reviewed major clinical journal as soon as possible after completed 90-day follow-up of the last randomised patient.

The 1-year mortality, the EQ-5D-5L outcomes, the RBANS evaluations, the pulmonary function tests, the health economic analyses, and the supplementary analysis of all ABG samples conducted will be submitted as separate publications to relevant peer-reviewed journals.

All results will be sought published, regardless of whether they can be considered positive, neutral or negative.

13 | STATUS

The trial was initiated on 20 June 2017. By 12 February 2020, 2477 patients have been randomised. The last patient is expected to be included mid-2020.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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