Aalborg 14 August 2019

HOT-ICU

Handling Oxygenation Targets in the Intensive Care Unit

Handling oxygenation targets in adults with acute hypoxaemic respiratory failure in the intensive care unit: A randomised clinical trial of a lower versus a higher oxygenation target

Protocol version 2.1, 14 August 2019

CRIC
Centre for Research in Intensive Care

14/11-2019

Professor, overlæge, ph.d.
Bodil Steen Rasmussen
Anæstesi og Intensiv Afdeling
Aalborg Universitetshospital

Applicable protocol registration numbers:
EudraCT number: 2017-000632-34
ClinicalTrials.gov Identifier: NCT03174002

In drafting of present protocol Copenhagen Trial Unit's Standard Operating Procedures were used

Table of content

Abstract

Background: Acutely ill adults with hypoxaemic respiratory failure admitted to the intensive care unit (ICU) are at risk of life-threatening hypoxia, and thus oxygen is administered. However, the evidence on the optimal level of oxygenation is of low quantity and quality with no firm evidence for benefit or harm. Importantly, liberal use of supplementary oxygen may increase the number of serious adverse events including death.

Objectives: To assess the benefits and harms of two targets of partial pressure of oxygen in arterial blood (PaO_2) in guiding the oxygen administration in acutely ill adults with hypoxaemic respiratory failure at ICU admission.

Design: We will conduct an investigator-initiated, pragmatic, outcome assessment blinded, international, multicentre, randomised parallel-group trial of two targets of PaO_2.

Inclusion and exclusion criteria: We will assess eligibility of all acutely admitted adult ICU patients who: (1) are receiving supplemental oxygen with a flow of at least 10 L per minute in an open system or a fraction of inspired oxygen (FiO_2) of at least 0.50 in a closed system, including invasive ventilation, non-invasive ventilation or continuous positive airway pressure, (2) have an arterial line; AND (3) are expected to receive oxygen administration for at least 24 hours in the ICU. We will exclude patients fulfilling one or more of the following: 1) cannot be randomised within 12 hours of ICU admission, 2) receive chronic mechanical ventilation for any reason, 3) use of home oxygen therapy, 4) have previously been treated with bleomycin, 5) have had organ transplant within current hospital admission, 6) withdrawn from active therapy or brain death is deemed imminent, 7) are pregnant, 8) are poisoned with carbon monoxide, cyanide or paraquat , 9) have methaemoglobinaemia, 10) expected use of hyperbaric oxygen for any reason, 11) have sickle cell disease, 12) consent cannot be obtained according to national regulations, OR 13) previously randomised into the HOT-ICU trial.

Intervention: Oxygen administered to achieve a PaO_2 target of 8 kPa (60 mmHg) or a PaO_2 target of 12 kPa (90 mmHg) during ICU stay for a maximum of 90 days.

Outcomes: Primary outcome: Mortality 90 days after randomisation. Secondary outcomes: serious adverse events in the ICU, days alive without organ support and days alive out of hospital in the 90-day period, and mortality, health-related quality of life, cognitive function and a health economic analysis at 1-year after randomisation.

Trial size: With an expected 90-day mortality of 25% in the control group and in order to detect or reject a true 20% relative risk reduction (5% absolute risk reduction), a total of 2928 patients are required with a maximal type 1 error of 5% and type 2 error of 10%.

Time schedule:

January 2017 – April 2017: Governance approval applications, education of trial sites, and other preparations

May 2017: First Danish patient enrolled

September 2017: Commencement of enrolment in other countries

May 2019: Last patient enrolled

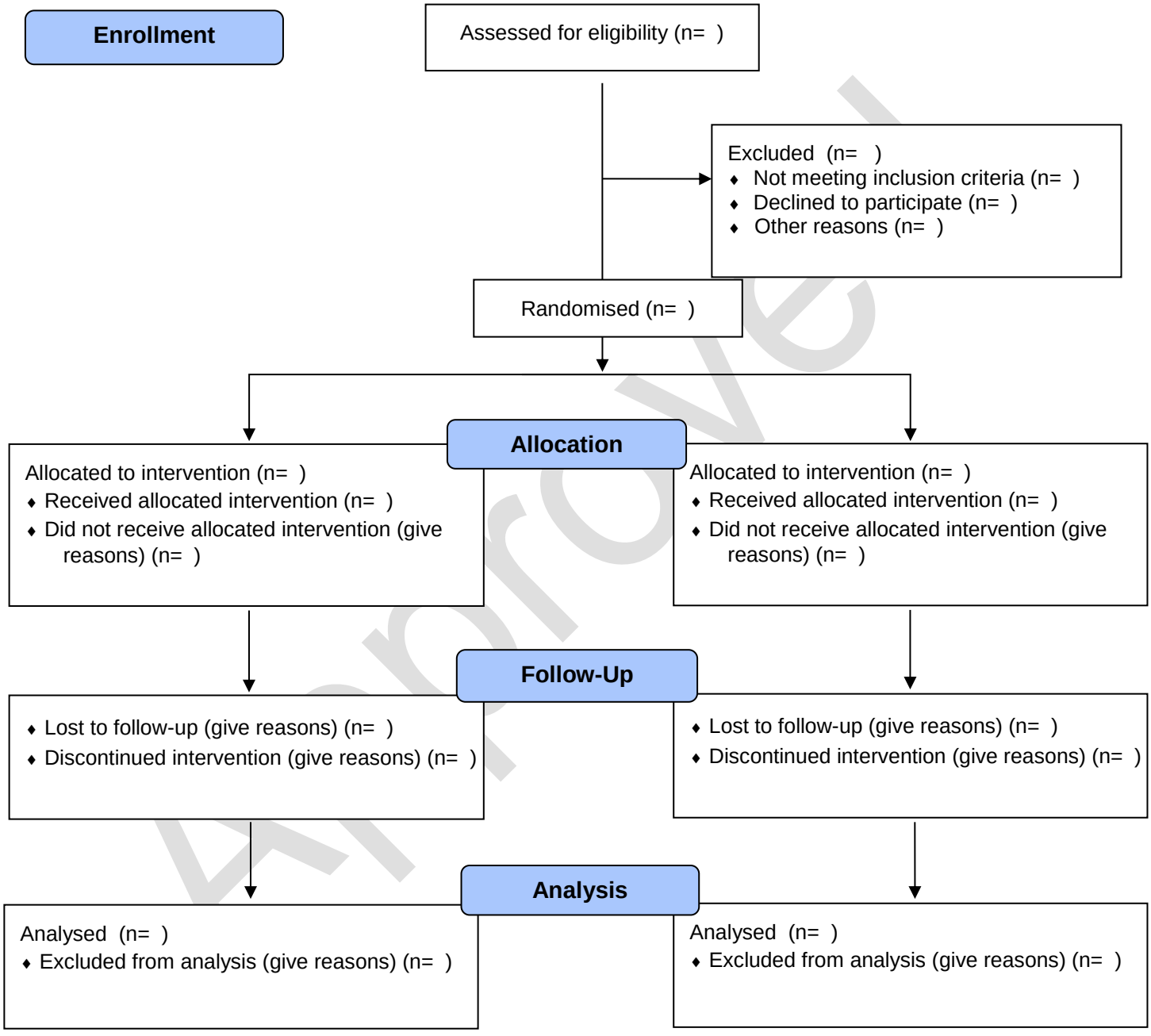
August 2019: Follow-up completed for the primary outcome

September - October 2019: Submission of the main publication

May 2020: Data analysis and submission of the long-term outcome publication

Trial flowchart

Flowchart (n=) will be filled in during or at the end of the trial.



Administrative information

The research program organisation is attached in *Appendix* 1.

HOT-ICU is the second of three planned clinical trials in the Centre for Research in Intensive Care, CRIC, established on a start-up grant from the Innovation Fund Denmark in 2015. Chair of the CRIC Executive Committee: Professor Anders Perner, Rigshospitalet, Denmark
Chair of the Scientific Steering Committee: Professor Bodil Steen Rasmussen, Aalborg University Hospital, Denmark
Project Manager: Cand.scient. Birgit Agerholm Larsen, CRIC, Denmark

Sponsor

Bodil Steen Rasmussen
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Hobrovej 18-22, 9000 Aalborg
E-mail: bodil.steen.rasmussen@rn.dk
Telephone: +45 9766 1864 or +45 2011 6272

Trial sites

Clinical sites:

ICUs in:

- Denmark
- Finland
- Norway
- Iceland
- Switzerland
- The Netherlands
- United Kingdom

Methodological and statistical sites:

Copenhagen Trial Unit (CTU), Rigshospitalet, Copenhagen, Denmark
Section of Biostatistics, University of Copenhagen, Denmark

Steering Committee

The Steering Committee consists of the Management Committee and the National Principal Investigators (*Appendix* 1)

Management Committee:

Sponsor:
Bodil Steen Rasmussen, Professor, MD, PhD
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark

Coordinating investigator:
Thomas Lass Klitgaard, MD
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark

Olav Lilleholt Schjørring, MD
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark

Anders Perner, Professor, MD, PhD
Department of Intensive Care
Copenhagen University Hospital Rigshospitalet
Denmark

Jørn Wetterslev, MD, PhD
Chief physician
Copenhagen Trial Unit (CTU)
Copenhagen University Hospital Rigshospitalet
Denmark

National principal investigators:

Jon Henrik Laake, MD
Department of Anaesthesia and Intensive Care
The National Hospital, University of Oslo
Norway

Marjatta Okkonen, MD, PhD
Department of Perioperative, Intensive Care and Pain Medicine
Helsinki University Hospital
Finland

Katrin Maria Thormar, MD
Department of Anaesthesia and Intensive Care
Landspitali University Hospital Reykjavik
Iceland

Martin Siegemund, MD, PhD, DMSci
Department of Intensive Care
University Hospital Basel
Switzerland

Frederik Keus, MD, PhD
Department of Critical Care
University Medical Centre of Groningen, University of Groningen
The Netherlands

Matt Morgan, MD, PhD
Cardiff University School of Medicine
College of Biomedical and Life Sciences
Cardiff, United Kingdom

Danish sites and local investigators:

Hospital	Local investigator
Bispebjerg Hospital Bispebjerg Bakke 23 2400 København NV	Christian S. Meyhoff Telephone: 22985042 Email: Christian.saltholt.meyhoff@regionh.dk
Herlev Hospital Herlev Ringvej 75 2730 Herlev	Anne Sofie Andreasen Telephone: 38683868 Email: anne.sofie.andreasen@regionh.dk
Herning Sygehus Gl. Landevej 61 7400 Herning	Robert Winding Telephone: 78432753 Email: robewing@rm.dk
Hillerød Hospital Dyrehavevej 29 3400 Hillerød	Morten Bestle Telephone: 48292017 Email: morten.bestle@regionh.dk
Hjørring Sygehus Bispensgade 37 9800 Hjørring	Andrei Ciubotariu Telephone: 97641133 Email: anci@rn.dk
Holbæk Sygehus Smedelundsgade 60 4300 Holbæk	Hans-Henrik Bülow Telephone: 5948 4105 Email: hhbu@regionsjaelland.dk
Holstebro Sygehus Lægårdvej 12 7500 Holstebro	Nilanjan Dey Telephone: 78432827 Email: nildey@rm.dk
Horsens Sygehus Sundvej 30 8700 Horsens	Lone Buus Telephone: Email: lonebuus@rm.dk
Hvidovre Hospital Kettegård Allé 30 2650 Hvidovre	Ulf Gøttrup Pedersen Telephone: 38623862 Email: ulf.goettrup.pedersen@regionh.dk
Kolding Sygehus Sygehusvej 24 6000 Kolding	Jane Stab Nielsen Telephone: Email: Jane.Stab.Nielsen@rsyd.dk
Køge Sygehus Lykkebækvej 1 4600 Køge	Valerij Khridin Telephone: Email: vkh@regionsjaelland.dk
Randers Sygehus Skovlyvej 1 8930 Randers	Thorbjørn Grøfte Telephone: 28494988 thorgroe@rm.dk
Rigshospitalet, Intensiv Terapiklinik 4131 Blegdamsvej 9 2100 København	Bjørn Brand Telephone: 35451043 Email: bjoern.brand@regionh.dk
Roskilde Sygehus Køgevej 7-13 4000 Roskilde	Thomas Hildebrandt Telephone: 47325056 Email: thi@regionsjaelland.dk
Slagelse Sygehus Ingemannsvej 18 4200 Slagelse	Susanne Andi Iversen Telephone: 58559000 Email: saiv@regionsjaelland.dk

Regionshospitalet Viborg Heibergs Allé 4 8800 Viborg	Christoffer Grant Sølling Telephone: 78445212 Email: chrsoell@rm.dk
Aalborg Universitetshospital Hobrovej 18-22 9000 Aalborg	Olav Lilleholt Schjørring Telephone: 97661921 Email: o.schjoerring@rn.dk
Aarhus University Hospital (Skejby), Intensiv Nord Palle Juul-Jensens Boulevard 8200 Aarhus N	Lars Henrik Nielsen Telephone: 78450000 Email: lanielse@rm.dk
Aarhus University Hospital (Skejby), Intensiv Øst Palle Juul-Jensens Boulevard 8200 Aarhus N	Hans Michael Betsch Telephone: 20588355 Email: hansbets@rm.dk

Finnish sites and local investigators (more to be added)

Marjatta Okkonen, MD, PhD

Department of Perioperative, Intensive Care and Pain Medicine

Helsinki University Hospital

Finland

Norwegian sites and local investigators (more to be added)

Jon Henrik Laake, MD

Department of Anaesthesia and Intensive Care

The National Hospital, University of Oslo

Norway

Icelandic sites and local investigators (more to be added)

Katrin Maria Thormar, MD

Department of Anaesthesia and Intensive Care

Landspitali University Hospital Reykjavik

Iceland

Swiss sites and local investigators (more to be added)

Joerg C. Schefold, MD, PhD, DMSci
Department of Intensive Care
University Hospital Bern
Switzerland

Martin Siegemund, MD, PhD, DMSci
Department of Intensive Care
University Hospital Basel
Switzerland

Dutch sites and local investigators (more to be added)

Frederik Keus, MD, PhD
Department of Critical Care
University Medical Centre of Groningen, University of Groningen
The Netherlands

English sites and local investigators (more to be added)

Matt Morgan, MD, PhD
Cardiff University School of Medicine
College of Biomedical and Life Sciences
Cardiff, Wales
United Kingdom

Data Monitoring and Safety Committee

Jean-Francois Timsit, MD, PhD
The Medical and Infectious Diseases Intensive Care Unit
Bichat Teaching Hospital
Paris Diderot University
Paris
France

Daniel De Backer
Department of Intensive Care
Erasme University Hospital
Brussels
Belgium

Andreas Kryger Jensen, Biostatistician, PhD
Department of Public Health, Section of Biostatistics
University of Copenhagen
Denmark

List of abbreviations

AE	Adverse events
AR	Adverse reactions
ARDS	Acute respiratory distress syndrome
ARR	Absolute risk reduction
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRIC	Centre for Research in Intensive Care
CRO	Contract research organisation
CTSM	Clinical Trial Supply Management
DMSC	Data Monitoring and Safety Committee
eCRF	Electronic case report form
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HBO	Hyperbaric oxygen
HOT-ICU	Hypoxaemic Oxygenation Target in the Intensive Care Unit
ICU	Intensive care unit
NYHA	New York Heart Association
PaO_2	Partial pressure of oxygen in arterial blood
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PEEP	Positive end-expiratory pressure
P-peak	Peak inspiratory pressure
P-plat	Plateau pressure
SPC	Summary Product Characteristics
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomised clinical trial
RRI	Relative risk increase
RRR	Relative risk reduction
SAE	Serious adverse event
SAR	Serious adverse reaction
SC	Steering Committee
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment

SUSAR	Suspected unexpected serious adverse reaction
TSA	Trial sequential analysis
TV	Tidal volume

1. Introduction and background

1.1 The patient population

Oxygen is essential to sustain human life and thus patients with acute hypoxaemic respiratory failure admitted to the intensive care units (ICU) are all treated with supplementary oxygen non-invasively or invasively to avoid life-threatening hypoxia. However, the appropriate 'dose' of oxygen in these acutely ill ICU patients is unknown. Clinical practice is guided by descriptive studies[1,2], three small randomised clinical trials (RCT)[3-5] and small interventional trials[6,7] only, and there is a worldwide tendency towards a liberal use of oxygen[8-16].

ICU patients in general and patients with acute respiratory failure needing mechanical ventilation in particular represent a significant burden. Annually, 13 to 20 million patients are mechanically ventilated in ICUs worldwide[17] with an overall in-hospital-mortality of 35 %[18]. Moreover, markedly reduced health related quality of life scores and physical deficits are seen up to 5 years after critical illness[19,20] with the most pronounced limitations seen in those patients who required mechanical ventilation[21,22] and especially in those who suffered acute respiratory distress syndrome (ARDS)[23].

1.2 Current treatment

In acutely ill patients admitted to the ICU, high levels of oxygen administration with or without mechanical ventilation is most often required to correct hypoxaemia measured as low arterial oxygen saturation (SaO_2) or low partial pressure of arterial oxygen (PaO_2). The normal PaO_2 is 10.7 to 13.3 kPa (80 to 100 mmHg) at sea level with a standard atmospheric oxygen fraction of 0.21[24,25] and a corresponding normal SaO_2 of 94 to 98 %[25-27]. These normal values are commonly used as the accepted oxygenation targets in ICU patients independent of the requirement of a higher fraction of inspired oxygen (FiO_2).

Hypoxaemia leading to low tissue oxygen tension (PO_2) is associated with increased mortality[8,10]. However, the 'critical' tissue PO_2 defined as the value below which oxidative cellular metabolism fails is not measurable in daily clinical practice, but it is as low as 0.13 kPa (1 mmHg) in isolated mitochondria[28]. Therefore, as only global oxygenation can be measured, the liberal use of oxygen is likely to provide a wide buffer of safety against life-threatening hypoxia. However, accumulating evidence of potentially harmful effects of hyperoxaemia challenge the liberal use of oxygen in ICU patients.

Hyperoxia is not precisely defined but is found only when FiO_2 is above 0.21. This places airway lining cells and alveoli at the greatest risk for hyperoxic cytotoxicity in patients given supplemental oxygen. Patients with acute hypoxaemic respiratory failure often require mechanical ventilation, this being a lifesaving intervention. However, in itself mechanical ventilation is deleterious to the lung tissue. Therefore, lung protective ventilation is recommended to avoid additional trauma to the lung with guidelines prescribing optimal pressure, volume, frequency and ratio between inspiration and expiration, but no recommendations for oxygen are given[29-33]. This is noteworthy, as pulmonary oxygen toxicity has been described centuries ago[34]**.** Reducing the FiO_2 to the lowest tolerable limit should therefore be the target for oxygen administration in all patients.

At present, restrictive oxygen administration is only recommended in two patient categories. In spontaneously breathing patients with hypoxaemic hypercapnic respiratory failure, most often being patients with chronic obstructive pulmonary disease (COPD), it is recommended to use the lowest possible FiO_2 to target a peripheral oxygen saturation (SpO_2) from 88 to 92 % or a PaO_2 from 7.3 to 10 kPa (55-75 mmHg)[27,35]. In ARDS patients being mechanically ventilated in the ICU the oxygenation target is recommended to be 7.3 to 10.7 kPa (55 to 80 mmHg)[29,30].This oxygenation target is not based on solid evidence, and is not included in clinical guidelines on mechanical ventilation in ARDS[33]. Nevertheless, the oxygenation target of 7.3 to 10.7 kPa (55 to 80 mmHg) is not limited to ARDS patients. It is often referred to as being the best guidance for oxygenation targeting in mechanically ventilated ICU patients in general[32,36,37]. In clinical practice however, oxygen is administered liberally and a large proportion of ICU patients worldwide are definitely hyperoxaemic with PaO_2 levels above the upper limit of the normal range of 13.3 kPa (100 mmHg) while on supplementary oxygen[8-16,38]. Moreover, several studies have shown that the observed oxygenation in ICU patients exceed the self-reported preferences among intensive care physicians and nurses[39-41].

1.3 Trial interventions

To define the oxygenation targets in the present RCT, we have chosen to use PaO_2 levels as targets over SaO_2 or SpO_2. This choice is based on the fact that the level of hyperoxaemia is uncontrollable if using only the SaO_2 or SpO_2 due to the sigmoid shape of the oxygen dissociation curve[42]. Recent meta-analyses of hyperoxaemia in adult critically ill ICU patients

confirmed this with a wide range of PaO_2 from 11.3 to 64.9 kPa (85 to 490 mmHg) corresponding to a narrow range of SaO_2 from only 96 to 100 %[1,2].
The oxygen content in the blood is only marginally lower at oxygenation targets of 8-10 kPa as compared with higher PaO_2 targets above 12 kPa due to the flatness of the upper part of the oxygen dissociation curve[28,36,42-44]. Moreover, as the oxygen flows through blood and tissues any difference in PaO_2 is diluted, and at the mitochondrial level, it is almost obliterated in normoxic as well as in hyperoxic conditions[28]. Furthermore, by being closer to the "break" on the oxygen dissociation curve, usually described as around 8.0 kPa, the possible oxygen delivery in tissues may actually be enhanced due to increased release of oxygen from haemoglobin at lower PaO_2 levels[42]. A shift of the haemoglobin dissociation curve to the right caused by high temperature or low pH impairs oxygenation in the lungs but aids release of oxygen delivery to the tissues. Whether these effects in combination will increase or decrease tissue PO_2 is not known. Noteworthy, oxygen delivery to tissues is not only governed by arterial oxygenation but also by cardiac output and haemoglobin concentration.

Hypoxia as well as hyperoxia produces detrimental effects at the cellular level[34]. Currently oxygen is used liberally, however, increasing evidence supports several potential harmful effects of hyperoxia; i.e. direct/indirect cellular damage mediated by reactive oxygen species (ROS)[45-49], especially in the lungs; hyperoxic derived vasoconstriction[50,51] with following paradoxical risk of tissue hypoxia; and formation of pulmonary absorption atelectasis with increased pulmonary shunt[52-54]. Furthermore, tissue and cellular adaptations at low PaO_2 occur through enhancement of oxygen delivery and lowering of tissue oxygen consumption. These adaptations have been proposed to happen in critically ill patients in the same manner as in healthy persons at altitude adding a possible defense against any negative effects of hypoxaemia[55].

Interventional before and after studies

Two relevant interventional before and after studies have been published.[6,7]. In three Dutch ICUs a two-step implementation of a conservative oxygenation strategy of a PaO_2 range of 7.3 to 11.5 kPa (55 to 86 mmHg) or a SpO_2 of 92 to 95 % was evaluated in 15.045 ICU patients of whom 81.8 % were mechanically ventilated during the ICU admission[7]. In an Australian ICU, a before and after study of implementation of a conservative oxygenation strategy with a target SpO_2 of 90 to 92 % during mechanical ventilation included 105 patients[6]. In both studies, the

implementation of conservative oxygenation targets was feasible and without apparent adverse outcomes as compared to the former liberal oxygenation strategies[6,7].

Meta-analyses and RCTs

A meta-analysis from 2014 on permissive hypoxaemia versus normoxaemia in mechanically ventilated critically ill patients failed to identify any RCT or quasi-RCTs[56]. Since then, two small RCTs have been published[4,5]. In the Panwar trial[4], 103 mechanically ventilated ICU patients were randomised to either a SpO_2 target of 88 to 92 % or a SpO_2 target of 96 % or above. In the Girardis trial[5], 434 patients with an expected length of stay in the ICU of 72 hours or longer were randomised to either a SpO_2 target of 94 to 98 % or one of 97 to 100 %; 70 % of these patients were mechanically ventilated. The Panwar trial[4] indicated no outcome differences between the two groups, while the Girardis trial[5], observed a higher mortality in the conventional SpO_2 group as compared to the conservative SpO_2 group. The latter trial was stopped prematurely due to a violent earthquake after the results from the resulting unplanned interim analysis were known. A French RCT, the Hyper2S trial (NCT01722422)[57], designed as a bi-factorial trial comparing a FiO_2 of 1.0 versus standard care and hypertonic versus isotonic intravenous saline in mechanically ventilated patients with septic shock was prematurely stopped after inclusion of 434 patients due to a 9% absolute increase in mortality in the hyperoxic group as compared to the standard care group, but the difference was not statistically significant at the 5% level (unpublished, but presented at ICU congresses). Finally, no difference was found in outcomes in a small pilot RCT of 34 spontaneously breathing COPD patients admitted to the ICU and randomised to a higher (>9.0 kPa) versus a lower (>6.6 kPa) oxygenation[3]. None of these trials were powered to detect or refute a clinically meaningful difference in mortality and all carried high risk of bias. Thus results from large trials with low risk of bias are needed. In a preliminary report of the results from a systematic review (ACE350 protocol for a systematic review of Effects of higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation in intensive care patients. A preliminary summary of the systematic review results) a meta-analysis of the effect of low versus high oxygenation targets on all-cause mortality in the three trials published so far, the point-estimate of the intervention effect was 23% relative risk reduction (RRR). However, this reduction in mortality was not statistically significant in a random-effects model and the required information size of 4,697 to detect or reject a 23% RRR was far from being reached, with only 571 participants being randomised so far (see *Appendix* 10).

There are two other meta-analyses of hyperoxaemia versus normoxaemia in ICU patients[1,2]. Both studies report a large degree of heterogeneity among the included studies, which encompass observational studies and interventional trials, but no RCTs. An association between hyperoxaemia and increased mortality was found in ICU patients overall[2], in patients with stroke[1,2], traumatic brain injury[1] and in those resuscitated from cardiac arrest[1,2,58].
Three RCTs on oxygenation targets in critically ill ICU patients are ongoing; 1) Evaluating the effects of two approaches to oxygen therapy in ICU patients requiring life support (mechanical ventilation), the ICU-ROX study (ACTRN12615000957594) comparing a standard regime versus a conservative approach with SpO_2 90-97 % in mechanically ventilated patients started in September 2015. A total inclusion of 1000 patients is planned and the primary outcome is ventilator-free days at day 28; 2) Liberal oxygenation versus conservative oxygenation in ARDS, the LOCO2 study (NCT02713451) comparing a liberal oxygenation target (PaO_2 12-14 kPa (90-105 mmHg) and $SpO_2 \geq$ 96 %) versus a conservative oxygenation target (PaO_2 7.3-9.3 kPa (55-70 mmHg) and SpO_2 88-92 %) started in June 2016. A total inclusion of 850 mechanically ventilated patients is planned and the primary outcome is 28-days mortality; 3) Optimal oxygenation in the Intensive Care Unit, the O2-ICU trial (NCT02321072) comparing a liberal oxygenation target (PaO_2 16 (14-18) kPa (120 (105-135) mmHg)) versus a conservative oxygenation target (PaO_2 10 (8-12) kPa (75 (60-90) mmHg)) in patients admitted to the ICU with at least two positive Systemic Inflammatory Response Syndrome (SIRS) criteria started in February 2015. Inclusion of a total of 385 patients is planned and the primary outcome measure is the cumulative daily delta Sequential Organ Failure Assessment (SOFA) score from day 1 to day 14. The results of these studies and new studies will be followed.

Clinical data on the control intervention
To keep the PaO_2 within the normal range it is necessary to increase the FiO_2 above 0.21 and thereby inducing a risk of tissue damage caused by oxygen toxicity. However, there is still a lack of quantitative and qualitative evidence of a high PaO_2 being superior than a low PaO_2 as well as to define the optimal oxygenation targets for hypoxaemic patients admitted to the ICU.

1.4 Adverse effects of oxygen

Some groups of patients may be more vulnerable to relative hyperoxaemia. The largest of these groups are patients with COPD in which relative hyperoxaemia with PaO_2 above10 kPa (75 mmHg) due to hyperoxic derived ventilation/perfusion (V/Q) mismatch[59-63] and/or a hypoxia-based respiratory drive[64,65] can cause or augment hypercapnic respiratory failure[27].

Hyperoxaemia has been shown to be associated with worsened clinical outcomes in spontaneously breathing COPD patients[27,66,67]. However, the evidence of a clinical detrimental effect of high level normoxaemia in COPD patients is very scarce[66], only one large RCT[68] has evaluated the effect of a titrated oxygenation strategy versus conventional high flow oxygen supplementation on mortality in COPD patients. In this RCT higher mortality was observed in the conventional versus the titrated group. This trial was conducted in a prehospital setting and allocation ceased upon hospital admission, therefore the level of monitoring was far from what would be seen in an ICU-setup. Furthermore, the level of oxygen supplementation in the conventional oxygen group in this trial was higher than what is necessary to achieve the high PaO_2 target of 12.0 kPa in our control group. In the only RCT on higher versus lower oxygenation targets in spontaneously breathing patients with COPD in exacerbation that has actually been conducted in an ICU-setup[3], no difference between groups in mortality or in the use of mechanical ventilation was found. Furthermore, there were no differences in $PaCO_2$ or arterial pH in spite of achieved mean PaO_2 of 12 kPa to 15.5 kPa in the high target oxygenation group versus mean PaO_2 of 8.5 to 10 kPa in the low target oxygenation group. In addition, most patients admitted to an ICU with an exacerbation of COPD will be treated either with invasive or non-invasive mechanical ventilation and in spontaneously breathing but invasively or non-invasively ventilated COPD patients, at very high FiO_2s ranging from 0.70 to 1.0 no[69-72] or only a minimal[73,74] tendency towards carbon dioxide (CO_2) retention with no respiratory acidosis has been described. This indicates that high FiO_2 during any kind of mechanical ventilation in COPD patients can be considered safe. Thus, whether a PaO_2 within the upper part of the normal reference interval is deleterious for COPD patients admitted to an ICU, monitored and possibly mechanically ventilated, has to be elucidated.

Non-hypoxic patients with ongoing myocardial ischemia may also be vulnerable to supplementary oxygen. A small double-blinded RCT, published in 1976, showed that excessive oxygen supplementation resulted in increased levels of markers of myocardial damage[75]. This finding were recently confirmed in a larger RCT, the AVOID trial[76], in which 441 non-hypoxic patients with ST-elevation myocardial infarction were randomised pre-hospitally to receive either conventional oxygen therapy through a facemask with 8 L pure oxygen per minute or no oxygen. The ‘no oxygen group’ had reduced levels of markers of myocardial damage and a lower rate of recurrent myocardial infarction[76]. Furthermore, a secondary descriptive analysis revealed a proportional association between increasing levels of oxygen exposure and rise in the markers of myocardial damage[77]. The mortality, however,

were not affected, and newly published meta-analyses of oxygen administration to patients with acute myocardial infarction, which included the AVOID trial, also indicated no difference in mortality[78-80].

No adverse reactions of normobaric oxygen are described in the international Summary Product Characteristics (SPC) for medical oxygen: Air Liquide, Healthcare[81]; BOC, A member of the Linde Group[82]. However, it is recommended to use the lowest level of oxygen administration to limit the toxicity of oxygen. In the Danish SPC (*Appendix* 5) three adverse reactions are listed; i.e. atelectasis and pleuritis noted as a not common adverse reactions and ARDS noted as very uncommon adverse reaction. All these three adverse reactions are common in patients admitted to the ICU with acute hypoxaemic respiratory failure. It will not be possible to distinguish whether these adverse reactions are due to the pathophysiology of the disease or caused by the administration of oxygen, but any meaningful differences in the rates of atelectasis or the severity of ARDS will be captured in HOT-ICU by the daily registrations in the ICU (see *Appendix 2*).

1.5 Risks and benefits

Since supplementary oxygen is a well-established intervention and the two targets of PaO_2 are within the presently recommended ranges there will be no additional risk for patients included in the HOT-ICU trial. None of the oxygenation strategies are proven the best, and clinical practices vary widely[8-16,38]. Likewise, any benefits or harms in either arm cannot be known with the present available evidence and needs to be elucidated in the setting of a large RCT.

1.6 Ethical justification and trial rationale

As described in former sections, there is no firm evidence from systematic reviews or single large RCTs with low risk of bias on the potential benefits or harms of lower versus higher oxygenation targets in adult ICU patients with acute hypoxemic respiratory failure. Oxygen is extensively administered with a great divergence in preferences regarding the level of oxygen administration[39-41], but with a general tendency towards liberal oxygen administration despite lacking evidence[8-16]. Moreover, self-reported preferences seem to be contradictive to the liberal oxygen approach[41]. In addition, there is a lack of guidelines on oxygenation targets in critically ill ICU patients. All these facts underline the need for robust and trustworthy evidence

in the form of large RCTs. Three small scale RCTs[3-5] have rectified that studies of restrictive versus liberal oxygenation targets in ICU patients are feasible and ethically justified as the present point estimate of the intervention effect of targeting a conservative oxygen target seems to reduce mortality even though this is not statistically significant (see *Appendix* 10).
Patients with known conditions or diseases where supplemental oxygen administration is either contraindicated or has to be given with precautions or where high FiO_2 is strictly indicated will be excluded from the HOT-ICU trial, including those previously treated with bleomycin, carbon monoxide poisoning, cyanide poisoning, methaemoglobinaemia, paraquat poisoning, and sickle cell disease. We will also exclude those in whom use of hyperbaric oxygen is expected, patients using oxygen or mechanical ventilation at home, patients with organ transplant during current hospital admission, pregnant women, patients in whom withdrawal of active therapy or brain death is deemed imminent and if consent according to national regulations cannot be obtained.
Oxygen is a part of the air that all humans breathe and is essential for survival. Patients admitted to the ICU often fail to oxygenate their blood sufficiently to meet normal values of PaO_2 and therefore it has been practice for decades to increase the FiO_2 with the aim to restore or at least increase PaO_2. Increasing evidence has been produced that questions whether supranormal values of PaO_2 above the upper normal level of 13.3 kPa (100 mmHg) as well as high levels of FiO_2 (≥0.50) when PaO_2 remains normal or low, have sufficiently positive effects to outweigh possible serious adverse effects (SAE) including excess mortality[1,2,5,57,83]. Nevertheless, there is profound diversity in the practice of administering oxygen in ICU's worldwide[8-13,15,16,38] and the true effects of different targets of PaO_2 on mortality, health related quality of life (EuroQoL, EQ-5D-5L and EQ-VAS), SAEs, and use of life support in the ICU is unknown. Based on the knowledge acquired so far both a target PaO_2 of 8 kPa and a target PaO_2 of 12 kPa would not a priori be considered beneficial or harmful, however, which of the targets that perform best, or whether they perform equally good, on the outcomes of mortality, EQ5D-5L, SAE, and use of life support in the ICU has to be investigated in a large, pragmatic, randomised trial with minimised risk of bias.
Each patient in the trial will likely benefit from the tight titration of oxygen by the clinical staff in all trial participants because of the potential harm from uncontrolled, liberal oxygen therapy.

All patients will be temporarily incapacitated because of severe illness or as a consequence of the treatment. We cannot perform the trial in competent patients, because patients with acute hypoxaemic respiratory failure admitted to the ICU will be cognitive affected due a deranged

gas exchange, severe critical illness and due to concomitant treatment with sedatives and analgesics. To perform clinical trials with the goal of improving the outcome for acutely hypoxic ICU patients, it is necessary to enroll patients before obtaining their informed consent.
Consent will be obtained according to national regulations, which in Denmark is by proxy (see *Appendix* 6). Informed consent before randomisation will be obtained from one independent physician and as soon as possible thereafter from the patient's next-of-kin, another independent physician and the patient her-/himself. The consenting party will be provided with written and oral information about the trial, so he/she is able to make an informed decision about participation in the trial. Written information and the consent form will be subjected to review and approval by the ethical committee system according to national law in all participating countries. The consenting party can at any time without further explanation withdraw consent.
The process leading to the achievement of consent may differ in the participating countries, and will be described and comply with all applicable regulations in the respective country.
A biobank will not be established.

1.6.1 Outcome considerations

Given the high mortality rates in ICU patients[84] and mechanically ventilated patients in particular[18], the possibility to affect mortality by interventions in the ICU is high, especially for interventions in such a pivotal area as oxygen administration. Therefore, the potential to improve treatment of acutely ill patients through this trial is high and hence the research question is in the public's interest. The design of the trial will minimise the risk of systematic errors and the trial will provide information on beneficial and/or harmful effects of either a lower or a higher oxygenation target. Only mortality as the primary outcome will weigh the totality of the potential positive and negative effects of these strategies.
Furthermore the rationales for choice of outcomes are:

1. Mortality were not the primary outcome in the first single RCT[4] conducted on the subject, and the sample size was far too small to evaluate mortality, making a type 2 statistical error inevitable. The second single RCT[5] was prematurely stopped due to an earthquake in the region making it underpowered. It did indicate an increased mortality in the conventional, liberal oxygenation group and also higher numbers of patients with shock, liver failure and bacteremia in this group compared to a group receiving more conservative oxygen administration. However, since the study was underpowered, no solid evidence on mortality

exists. Noteworthy, the advantageous low oxygenation target in the conservative group in this second RCT corresponds to the high oxygenation target in our control group. The Hyper2S trial[57] was stopped early due to futility and potential excess mortality in the high oxygen supplementation group. A systematic review have suggested reduced all-cause mortality with a low oxygen target strategy (see *Appendix* 10).

2. Meta-analyses on hyperoxaemia have shown associations between hyperoxaemia and mortality in critically ill patient populations[1,2]. Thus, a high oxygenation level is a risk factor for mortality.
3. Other important patient-centered outcomes will be secondary outcomes including long-term mortality, EQ-5D-5L and EQ-VAS and cognitive function. Composite outcomes of the degree of life support as days alive without the use of respiratory support, renal replacement or vasopressor/inotropic therapy, days alive out of hospital and ischaemic events in the ICU seem valid to assess and will also be secondary outcomes. The recommendation for using composite outcomes is to report individual components as well, and we will do that in a supplement to the primary publication.

The primary outcome measure will be mortality of all causes within 90 days of randomisation (for details see section 7.1). Secondary outcomes will be as described in section 7.2.

1.6.2 Power calculation considerations

In order to detect or reject a true 20% relative risk reduction, achieving a maximal type 1 error of 5% and type 2 error of 10%, we aim for randomisation of 2928 patients. The sample size estimation is based on a mortality within 90 days for the patients included in the control group (target PaO_2 of 12 kPa) of 25%[38,85] and randomisation 1:1 to the two groups. We will be able to detect or refute an absolute risk reduction of 5%-point or more, corresponding to a number needed to treat of 20 or less.

The primary analyses will all be done in the intention-to-treat population and we will perform per-protocol analyses excluding patients with one or more major protocol violation.

A predefined detailed statistical analyses plan including models for all secondary outcomes will be published before randomisation of the last patient. To gain adequacy of power in the

statistical analysis we will adjust the primary analyses for the stratification variables, and present the intervention effect expressed as relative risk (RR) with 95% confidence intervals in the overall population as well as in the planned subpopulations listed in 11.2.1. Power calculations for secondary outcomes are described in *Appendix 9*.

1.7 Trial conduct

The trial will be conducted in compliance with a published trial protocol, the Helsinki Declaration in its latest version[86], the good clinical practice (GCP) guidelines[87], and national laws in the participating countries. The protocol will be registered on www.clinicaltrials.gov and at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) before trial start. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible. Enrolment will start after approval by the ethical committees, medicines agencies, data protection agencies and health authorities in the participating countries. A manuscript with main points of the protocol including description of design, rationale and analysis plan will be submitted to a peer-reviewed journal in English language.

1.7.1. Schedule for study conduct including time line for key study milestones

- First patient randomised (or study subject): 1st of May 2017
- Last patient randomised (or study subject): 31st of April 2019
- Last patient 90 days follow-up: 31st of July 2019
- End of trial (including follow-up and data analysis): June 2020

1.7.2 Description of recruitment strategy

Having extensive experience with the recruitment of patients into international trials[88,89] we will use our established network of ICUs to recruit sites. In these, we will screen all patients admitted to the ICUs fulfilling the inclusion criteria. Incentive strategies will include case money paid for the extra work of randomisation, registration, and follow-up of patients in the trial, a pragmatic eCRF registering only what is absolutely needed to know, with a user friendly interface, use of public databases to retrieve outcomes whenever possible and a predefined publication strategy granting authorship to active sites according to the Vancouver

statement[90]. We will encourage investigators during meetings and with newsletters and will conduct visits to all sites guiding them in recruitment, registration, and data retrieval within the trial period.

We expect 50 ICUs in Europe to participate (Denmark, Norway, Finland, Iceland, the Netherlands, Switzerland, and the United Kingdom). On average each site is estimated to randomise 100 (expected range from 50 to 500) patients during the 2 years of enrolment. We will monitor the inclusions rate and include additionally ICUs if needed.

1.7.3 Assignment of the intervention

We will screen all patients who fulfill the inclusion criteria in the eCRF. Those not fulfilling any exclusion criteria will be randomised through a central website produced by Copenhagen Trial Unit (CTU) linked to eCRF. An oxygen target of PaO_2 will be assigned via the website to each patient after registration of the stratification variables. The site investigator or his/her delegate will implement the assigned oxygenation target for each patient and oversee that the administration of oxygen, being the lowest FiO_2 accomplishing the desired target (a PaO_2 of 8 kPa (60 mmHg) or a PaO_2 of 12 kPa (90 mmHg)), is given to the patient. Maintenances of the oxygenation target will be controlled by the sampling of arterial blood by the ICU nurse for immediate testing in a standard arterial blood laboratory machine.

2. Trial objectives and purpose

To assess the benefits and harms of two oxygenation targets to guide oxygen administration in adult, acutely ill ICU patients with hypoxaemic respiratory failure.

3. Trial design

3.1 Trial design

HOT-ICU is an investigator-initiated, pragmatic, international, multicentre, randomised, parallel group trial targeting two levels of PaO_2 using computer generated allocation sequence, centralised and stratified allocation, and blinding of outcome assessors and statisticians. Adult patients acutely admitted to ICUs in Europe will be randomised to a target of 8 kPa or a target of 12 kPa of PaO_2 during ICU stay.

3.2 Randomisation

Patients will be screened for enrolment as soon as possible and no longer than twelve hours after ICU admission (see section 3.5). This will be ensured through implementation of trial methodology at trial sites.

1:1 randomisation will occur centrally through the web-based eCRF-system according to a computer-generated allocation sequence list using varying block size and the following stratification variables: 1. trial site as per ICH-GCP[91], 2. known COPD, because the intervention effect may differ in these patients as compared to the remaining patients and 3. active haematological malignancy to ensure balance in these patients between the two groups, because they have very high mortality[88]. Each patient will be allocated a unique patient-screening number.

3.3 Blinding

The allocation group will not be blinded for the investigators and the clinicians as this is practically impossible as both arterial blood samples, data from pulse oximetry, oximeter scales, and the randomised allocation will and should be common knowledge in the ICU. Therefore, the members of the management committee will not be involved in the daily clinical decision makings of included patients.

The outcome assessment will be blinded (e.g. registry based assessment of life-support, hospital stay and mortality and EQ-5D-5L and EQ-VAS). The statistical analyses will be done with the intervention groups masked i.e. coded as X and Y. Based on this masked analysis two conclusions will be drawn, one conclusion assuming X is the experimental group and Y is the control group, and one assuming the opposite. Two abstracts will be written and accepted by the Steering Committee (SC) before the blind is broken.

The members of the Data Monitoring and Safety Committee (DMSC) will remain blinded unless 1) they request otherwise or 2) the interim analysis has provided strong indications of one intervention being beneficial or harmful (a charter for the independent DMSC is attached as *Appendix* 3).

3.5 Participant timeline

We will strive to enroll patients as soon as they fulfill the inclusion criteria. Patients will be allocated to either of the two PaO_2 targets and will continue the allocated intervention until death in the ICU or discharge from the ICU with a maximum of 90 days after randomisation. If

the patient is readmitted to the ICU within 90 days after randomisation supplementary oxygen shall be given according to the allocated PaO_2 target.

4. Selection of participants

All patients referred to a participating clinical trial site will be considered for participation. Patients will be eligible for randomisation, if they fulfill all of the inclusion criteria and none of the exclusion criteria listed below (see *Appendix* 4).

4.1 Inclusion criteria

We will screen all patients who are:

- Acutely admitted to the ICU **AND**
- Aged ≥ 18 years **AND**
- Receives supplemental oxygen with a flow of at least 10 L per minutes in an open system including high-flow systems OR at least a FiO_2 of 0.50 in a closed system including invasive or non-invasive ventilation or CPAP systems **AND**
- Expected to receive supplemental oxygen for at least 24 hours in the ICU **AND**
- Having an arterial line for PaO_2 monitoring

4.2 Exclusion criteria

We will exclude patients who fulfil one or more of the following criteria:

- Cannot be randomised within twelve hours after present ICU admission
- Chronic mechanical ventilation for any reason
- Use of home oxygen
- Previous treatment with bleomycin
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death deemed imminent
- Fertile woman (< 50 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG
- Carbon monoxide poisoning
- Cyanide poisoning
- Methaemoglobinaemia
- Paraquat poisoning

- Any condition expected to involve the use of hyperbaric oxygen (HBO)
- Sickle cell disease
- Consent not obtainable according to national regulations
- Previously randomised into the HOT-ICU trial

4.3 Participant discontinuation and withdrawal

4.3.1 Discontinuation and withdrawal at the choice of the participant

The procedure of handling withdrawal of consent from a patient will follow national regulations and will be described for each participating country.

The Danish procedure:

A patient, who no longer wishes to participate in the trial, can withdraw his/her consent at any time without need of further explanation and without consequences for further treatment. If a patient is still incapacitated, he/she will be withdrawn from the trial at any time if consent is withdrawn by the person(s) who have given proxy-consent.

In order to limit the amount of missing data we plan to keep and collect as much data from each withdrawn patient as possible. Therefore, if possible, the investigator will ask the patient which aspects of the trial he/she wishes to withdraw from:

- Receiving the trial intervention only (allowing all data registration and follow-up)

OR

- Receiving the trial intervention AND further registration of daily and/or follow-up data

4.3.2 Discontinuation and withdrawal at the choice of the investigator

A patient can be discontinued from the trial intervention by the investigators at any time, if:

- The patient experiences intolerable adverse reactions suspected to be related to the trial intervention

In these cases, the collection of data will continue and full follow-up will be conducted. The patient will remain in the intention-to-treat population.

If an ineligible patient is randomised by mistake; i.e. patients who retrospectively are found not to fulfil the inclusion criteria OR patients who retrospectively are found to fulfil one or more of the exclusion criteria, the patient will continue in the trial and in the intention-to-treat population[92].

If the patient experiences a suspected unexpected serious adverse reaction (SUSAR) the trial intervention in this patient will be stopped; data registration will continue (see section 8). Patients who are transferred to another ICU will be regarded as discharged from the ICU unless the new ICU is an active HOT-ICU trial site. In any case, patients transferred to another ICU will be followed up for the primary outcome measure and as many of the secondary outcome measures as possible.

5. Selection and trial sites and personnel

5.1 Trial sites and setting

Trial sites will be ICUs in Europe. Only ICUs that have access to blood gas analyses (PaO_2) around the clock and that have continuous pulse oximetry as part of their standard monitoring will be accepted as trial sites. Trial sites are listed in the section 'Administrative information'. The section will be updated during the trial.

5.2 Trial personnel

All clinicians caring for patients in the participating ICUs will be eligible to screen patients and perform the interventions.
All participating ICUs will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for questions.

6. Trial interventions

6.1 Experimental intervention

To ensure measurements of PaO_2 only patients with an arterial line for collections of blood gas analysis are included. Continuous measurement of SpO_2 is part of basic monitoring in the participating ICUs. The experimental intervention will be an oxygenation target of a PaO_2 equal to 8 kPa (60 mmHg) with the purpose of reducing the FiO_2 and thus the potential oxygen toxicity. Results from the arterial blood samples will be registered in the eCRF as the highest and the lowest PaO_2 in intervals of 12 hours; i.e. 06:00 – 18:00 and 18:00 – 06:00. The corresponding SaO_2 and FiO_2 will be registered as well. Use of respiratory support on this day will be registered. Positive end-expiratory pressure (PEEP), peak inspiratory pressure (P-peak) and tidal volume (TV) will be registered at 08:00h if the patient is invasively ventilated here. If the patient is receiving non-invasive ventilation or mask CPAP, the CPAP pressure will

be registered at 08:00h. The total number of arterial blood samples will be registered. If the patient is readmitted to the ICU, the allocated intervention should be continued until final discharge from the ICU or the end of the 90-day trial period.
The PaO_2 is obtained by changes in FiO_2 and ventilator setting on the discretion of the treating clinicians. Full description of all registrations is given in *Appendix 4*.

6.2 Control intervention

The control intervention will be an oxygenation target of a PaO_2 equal to 12 kPa (90 mmHg). The monitoring and the intervention period will be identical to that of the experimental intervention.

6.3 Co-interventions

All patients in the trial will be given co-interventions as decided by the clinicians.

The registered co-interventions will be:

- Continuous treatment with vasopressor/inotropes (y/n) (daily in ICU)
- Renal replacement therapy (y/n) (daily in ICU and final date of therapy in the 90-day period)
- Number of units of red blood cells (daily in ICU)

ICU treatment and management in general will be at the discretion of the treating clinicians. However, we will endeavour to keep the allocated PaO_2 target in all patients during transportation to x-ray or procedures and also during surgical procedures. Preoxygenation with FiO_2 equal to 1.0 prior to or during endotracheal procedures such as bronchoscopy and tracheostomy, including suction should be avoided if at all possible. If not, the FiO_2 may be increased up to 1.0 for a maximum duration of 1 minute prior to endotracheal suction and for a maximum duration of 3 minutes prior to intubation at the discretion of the clinical team.

6.4 Concomitant interventions

All other interventions are allowed.

6.5 Intervention accountability

Oxygen is available bedside in all ICUs. Oxygen is a medical gas administered through oxygen dispensing systems. Oximeters measure the percentage of oxygen mixed with air or the FiO_2 administrated to each patients.

7. Outcomes

Detailed descriptions of all outcomes are given in *Appendix* 4.

7.1 Primary outcome

90-day mortality post-randomisation.

7.2 Secondary outcomes

- Number of patients with one or more SAEs in the ICU after randomisation; SAEs are defined as new episode of shock and new episodes of ischemic events including myocardial or intestinal ischaemia or ischemic stroke
- Days alive without the use of respiratory support, renal replacement therapy or circulatory support in the 90-day period
- Days alive out of the hospital in the 90-day period
- Mortality 1-year after randomisation
- EQ-5D-5L and EQ-VAS after 1-year after randomisation. Patients who have died will be assigned the lowest possible EQ-5D-5L and EQ-VAS score
- Cognitive function 1-year after randomisation as assessed using RBANS score in selected sites
- A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-effectiveness versus cost-minimisation analyses)

The power estimation of secondary outcomes are described in *Appendix* 9.The specific elements of the composite outcomes will be reported in a supplement to the primary publication.

7.3 Exploratory outcomes

To further qualify the findings of the primary analyses a mediation analysis exploring the degree to which the treatment effect is mediated through the sequence of measured PaO_2 will be performed.

Substudies will be encouraged as long as they do not hamper the completion of the main protocol and can be conducted after approval of the protocol by the SC. An exploratory study of blood and lung fluid metabonomics is already planned and will be performed at selected trial sites, as minimum at the ICU of the primary investigator, who has the expertise and manpower to perform NMR spectroscopy. Specific protocols will be send for approval before they will be included as part of the main study.

8. Safety

Patients admitted acutely to the ICU are critically ill with various degrees of organ dysfunctions. Several adverse events (AE) occur during the entire ICU stay and as such every organ system is daily systematically described in details in the patient file, including AEs and serious adverse events (SAEs). Specific SAEs will be registered in the eCRF; i.e. acute myocardial ischemia, acute ischaemic stroke, acute intestinal ischemia and shock. The ischaemic SAEs may be correlated to the oxygen administration in both the low PaO_2 group due to a relative hypoxaemia as well as in the high PaO_2 group due to oxygen induced arterial vasoconstriction. Therefore, the clinicians will be asked to notify in the eCRF whether these SAEs are caused or related to oxygen; i.e. related, possibly related or not related. If these SAEs are noted in the eCRF as being related or possibly related to oxygen the sponsor will be notified. The sponsor (or delegated party) will assess the relationship with oxygen and evaluate whether an adverse reaction (AR) or a severe adverse reaction (SAR) is present. The effect of oxygen administrated through the airways on the injured lung tissue and incidence of atelectasis will be continuously measured with registration of two PaO_2/FiO_2 ratios every 12 hours during the entire ICU stay (see *Appendix 2)* and followed carefully by the sponsor (or delegated party). If a SUSAR occurs the patient will be withdrawn from the study. Reasons for withdrawal in the eCRF includes a SUSAR and the clinicians will be asked to contact the sponsor immediately and to fulfil a formula included in the site master file and send it by email to the sponsor within 24 hours. Details of reporting are described in section 8.4.

8.1 Definitions

Adverse event (AE): any undesirable medical event occurring to a patient during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a patient during a clinical trial. ARs will not be registered in the HOT-ICU trial.

Serious adverse event (SAE): any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity.

Serious adverse reaction (SAR): any adverse reaction (as defined above) that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity.

Suspected unexpected serious adverse reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected. SUSAR will be defined as SARs suspected to be related to oxygen supplementation.

8.2 Risk and safety issues in the current trial

Oxygen is administrated to all adult ICU patients. Current clinical practice is likely liberal, but variation occurs. In Denmark, oxygenation targets vary from 8 to 14 kPa (60 to 105 mmHg)[38], and the target of this trial are therefore within those of current clinical practice.

The patients allocated to the lower target will be closer to critical levels of tissue oxygenation, but these levels are well below the 8 kPa[28-30]. Moreover, the trial participants will only be enrolled in ICUs using continuous monitoring of oxygen saturation, and ICU staff have vast experience in handling patients with lower levels of oxygen. We therefore consider the patient safety to be high in the HOT-ICU trial.

8.3 Adverse reactions and events

8.3.1 Recording of serious adverse reactions and events

If a patient experiences a SUSAR, the local investigator must report this without undue delay to the Sponsor (or delegated party) and the trial intervention will be stopped for this patient.
All SAEs according to the ICH-GCP definition will not be recorded as an entity, because the majority of critically ill patients will experience SAEs each day during their entire ICU stay and these will be registered by the clinician in charge in the patient files. The most important SAEs, i.e. ischaemic events and new episodes of shock, will be registered as secondary outcomes and others will be captured in the secondary outcome measures days alive without life-support. To ensure patient safety, the coordinating investigator will draw registrations of PaO_2, FiO_2 and the SAEs: new myocardial ischaemia, new intestinal ischaemia, and new ischaemic stroke from the eCRF and report them to the sponsor once a month, who will assess the possible relation to oxygen administration. These data will not be coupled to the interventional groups.
Patient charts, notes and lab reports will contain daily registrations of clinical data, which in ICUs are abundant. These data can be obtained on request from the medical authorities.

8.4 Reporting

Trial investigators are to report SUSARs without any delay to the sponsor, which in turn will report these to the Danish Medicines Agency no later than 7 days after the report has been received for fatal or life-threatening SUSARs. No later than 8 days after the reporting, the sponsor must inform the Danish Medicines Agency of relevant follow-up information on the sponsor's and the investigator's follow-up action to the reporting. Any other SUSARs must be reported to the Danish Medicines Agency no later than 15 days from the time when the sponsor is informed.
SUSARs should be reported according to the local requirements and regulations and Directive 2001/20/EC[93].
Once a year the sponsor will submit a list of all SARs that have occurred during the trial period as a well as a report on safety of the trial subjects to the Danish Medicines Agency.
The sponsor must notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter) or if earlier than planned, the reasons for stopping the trial must be given.
The results from the clinical trial including important AEs must be recorded on EudraCT.

9. Procedures, assessments and data collection

9.1 Inclusion procedure

9.1.1 Screening

All patients admitted to participating ICUs will be eligible for screening. In fertile women (< 50 years of age) a negative urine-hCG or plasma-hCG must be presented before enrolment.

9.1.2 Procedures for informed consent

Patients will be enrolled after consent is obtained according to the national regulations. The procedures will be described for each participating country. The procedure for Danish patients is described in *Appendix* 6.

9.2 Data collection

9.2.1 Method

Data will be obtained in eCRFs hosted in a database in CTU from a combination of patient files and national registers. An agreement between sponsor and CTU will be signed before the first patient is included. For patients transferred from a trial ICU to a non-trial ICU, data related to the outcomes of interest will be collected after transfer e.g. by national registers, phone calls and/or patient charts.

9.2.2 Timing

Appendix 7 shows an overview of the timing.

9.2.3 Variables

All variables are defined in *Appendix* 4

Baseline variables:

- Sex
- Date of birth
- Date of admission to hospital and date and time of admission to ICU
- Admission directly from the operating or recovery room after elective surgery (y/n)

- Admission directly from the operating or recovery room after emergency surgery (y/n)
- Patient height
- Respiratory support (invasive ventilation, non-invasive ventilation or CPAP) with measures of tidal volume, PEEP and P-peak, or CPAP pressure at randomisation
- PaO_2, SaO_2, and serum-lactate in the *last* arterial blood gas sample conducted within twelve hours *before* randomisation and the corresponding FiO_2 at this time
- Acute co-morbidities (pneumonia, septic shock, multiple trauma, stroke, myocardial infarction, cardiac arrest, intestinal ischaemia, traumatic brain injury, ARDS, renal failure)
- Chronic co-morbidities:

  - COPD (y/n)

  - History of ischaemic heart disease (y/n)

  - Chronic heart failure (y/n)

  - Active Haematological malignancy (y/n)

  - Active metastatic cancer (y/n)

  - Chronic dialysis (y/n)
- Variables for SOFA scoring 24 hours prior to randomisation (see *Appendix* 8)

Daily during ICU admission:

- Respiratory support on this day, specified as invasive or non-invasive mechanical ventilation or CPAP (closed systems) (y/n)
- PaO_2 highest and lowest values every 12 hours and corresponding SaO_2 and FiO_2
- Tidal volume, PEEP and P-peak or CPAP pressure at 08:00h if on respiratory support (closed systems)
- Highest lactate every 24 hours
- Circulatory support (infusion of vasopressor/inotropes) on this day (y/n)
- Any form of renal replacement therapy on this day (y/n)

- Acute myocardial ischaemia on this day (y/n)
- Acute ischaemic stroke on this day (y/n)
- Acute intestinal ischaemia on this day (y/n)
- Use of prone position in the ICU on this day (y/n)
- Use of inhaled vasodilators on this day (y/n)
- Use of extracorporeal membrane oxygenation in the ICU on this day (y/n)
- Cumulated number of arterial blood gas samples conducted
- Number of units of RBCs

Follow-up 90 days after randomisation

- Dead (y/n, if yes, date of death)
- Final date of renal replacement therapy if used (if used within the last week up till day 90, the therapy will be considered as being used for the full 90 days)

Follow-up 1 year after randomisation

- Death (y/n, if yes, date of death)
- EQ-5D-5L and EQ-VAS scores
- RBANS scores at selected sites

10. Data handling and record keeping

10.1 Data management

Data will be entered into an electronically, web-based eCRF, hosted at CTU, from medical files and national registers by trial personnel.

10.2 Confidentiality

Each patient will receive a unique trial identification number. Trial investigators will receive personal usernames and passwords to access the randomisation system and the eCRF. Each site will only have access to site specific data.
Data will be handled according to the National Data Protection Agency, and will be protected by the Danish national laws 'Loven om behandling af personoplysninger' and 'Sundhedsloven'.

10.3 Biobanking

No biobank will be formed.

10.4 Access to data

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived at trial sites for 15 years. The clean electronic trial database file will be delivered to the EudraCT Database and Zenodo (https://zenodo.org/about) and maintained for 15 years and anonymised if requested by the authorities.

11. Statistical plan and data analysis

90-day all-cause mortality is the primary outcome.

11.1 Sample size estimation and power calculations

11.1.1 Sample size estimation

Assuming a 90-day mortality of 25%[84,85] for acutely admitted ICU patients (α=0.05 (two-sided), and β=0.1) 2 x 1464 patients are required to detect a 20% relative risk reduction or increase (5% absolute risk reduction or increase) from this number.

11.1.2 Power estimations for secondary outcomes

The power estimations for the secondary outcomes are describes in *Appendix 9*.

11.2 Statistical methods

The primary analysis will be conducted in the intention-to-treat population being all randomised patients except those deleted due to withdrawal of consent[91,94,95]. Two sensitivity

analyses will be conducted including two per-protocol populations; i.e. 1) excluding all patients with a major protocol violation defined as the two registered PaO_2s in one 12-hour interval are either at least 1.0 kPa above the PaO_2 target if oxygen is administrated (FiO_2 above 0.21 or any oxygen flow) OR both at least 1.0 kPa below the PaO_2 target with concomitant FiO_2 below 1.0; 2) excluding all patients with a major protocol violation defined as the highest PaO_2 being at least 1.0 kPa above the PaO_2 target if oxygen is administered in four consecutive 12-hour intervals OR the lowest PaO_2 being at least 1.0 kPa below the PaO_2 target with a concomitant FiO_2 below 1.0 in four consecutive 12-hour intervals.
The primary analysis of the primary outcome (90 days mortality) will be a generalised linear model with a log-link and binomial error distribution adjusting for the stratification values listed in 3.2. Significance of the intervention will be assessed based on p-values form this regression and risk ratios with 95% confidence intervals are readily available from this regression. The primary analysis will be supplemented with Kaplan-Meyer plots (not accounting for stratification variables) and Cox proportional hazard models with adjustment for stratification variables. The primary analysis of all dichotomous outcomes at 90 days will compare the two intervention groups by binary logistic regression analysis with adjustment for stratification variables[96].

A secondary analysis of the primary outcome only will be performed adjusting for the stratification variables together with other known prognostic factors: age, active metastatic cancer, type of admission (medical, elective surgery or emergency surgery) and baseline SOFA score.
Further details will be provided in the predefined statistical analysis plan published before the last patient is included.

11.2.1 Pre-planned subgroup analyses

We will compare the primary outcome measure in pre-specified subgroups of patients with 1) shock at randomisation (y/n), 2) invasive mechanical ventilation at randomisation (y/n) 3) type of ICU admission (medical/elective surgical/emergency surgical), 4) known COPD at randomisation (y/n) and 5) known acute traumatic brain injury at randomisation.

11.2.2 Significance

A two-sided P value of less than 0.05 will be considered statistical significant.

11.2.3 Interim analysis

A data safety and monitoring committee (DSMC) will oversee the trial, having immediate and full access to all data in the trial database (via the eCRF), during the entire trial period. One interim-analysis will be performed after 50% of the planned sample size (1,464 patients) has been followed for 90 days, but the DSMC may conduct unplanned interim-analyses if relevant.

The DMSC will decide its own plan of monitoring and meetings. The charter for the DMSC (*Appendix* 3) defines the minimum of obligations and responsibilities of the DMSC as perceived by the SC, its relationship with other trial components, its membership, and the purpose and timing of its meetings.
The DMSC may recommend pausing or stopping the trial if group-difference in the primary outcome measure or SAEs are found in the interim analyses with statistical boundaries based on O-Brien Fleming alfa-spending function[97]. If an analysis of the interim data from the 1464 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the SC may stop the trial[91]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping the trial due to expected futility of showing a 20% RRR will not be an option as intervention effect less than 20% RRR of all-cause mortality may be clinical relevant as well.

11.2.4 Early stopping criteria

See previous section.

11.2.5 Accountability procedure for missing data/population for analysis

We will use an electronic case report form (eCRF) with a pragmatic design and incentive strategies to maximise complete registration in order to minimise the occurrence of missing data. If less than 5% of the data are missing on any primary or secondary outcome, a complete case analysis without input of missing values will be performed. If missing data are more than 5%, a blinded statistician will assess whether data are “missing completely at random” (MCAR criterion) based on a rational assessment of the pattern of missing data[98]. Little’s test will be

used if doubt remains [99]. If it is concluded that data are not ”missing completely at random”, multiple imputation using chained equations will be performed by creating at least ten input data sets under the assumption that the data are missing at random (MAR criterion)[100,101]. We will use outcomes and the most important baseline characteristics in the multiple imputation. The exact variables to be used to estimate the missing values will be outlined in the detailed statistical analysis plan; if multiple imputation is used, then the primary result of the trial will be based on the imputed data. The unadjusted, non-imputed analysis will also be made available. If multiple imputation is used, we will use a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the “best-worst-case” scenario it is assumed that all patients lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived, had no SAEs, ect.); and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived, have had SAEs, etc.). Conversely, in the “worst-best-case” scenario, it is assumed that all patients who were lost to follow-up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a beneficial outcome will be defined as the group mean plus two standard deviations (SD) of the group mean, and a harmful outcome will be defined as the group mean minus two SD of the group mean.

12. Quality control and quality assurance

The coordinating investigator will be responsible for organising the trial sites including education of local investigators, research nurses, and other trial site staff before the initiation of the trial. The education will be continuously documented and an annual investigator meeting will be planned.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of patients and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial patients.

12.1 Monitoring the intervention groups

The trial will be externally monitored following a monitoring plan developed in collaboration with the GCP Unit in Aarhus-Aalborg, which will coordinate the monitoring done by the local GCP units and/or monitors in all countries. A centralised day-to-day monitoring of the eCRF will be done by the coordinating investigator and his delegates.

13. Legal and organisational aspects

13.1 Finance

13.1.1 Trial funding

The HOT-ICU trial is funded by the Innovation Fund Denmark (4108-00011A) (5.642.428 DKr), the Danish Society of Anaesthesia and Intensive Care Medicine (DASAIM) (43.000 DKr), Obel Family Foundation (800.000 DKr), Regionernes Medicinpulje (575.000 DKr) and the ICU Symposium Hindsgavl (30.000 DKr). Additional funds are applied for from public and private foundations. The funding sources will have no influence on the trial design or conduct or data handling, analysis or publication.

13.1.2 Compensation

The trial sites will be given DKr 1500 (200 Euro) in case money for each patient with full data entry including 90-day follow-up to compensate for the increased workload participation infers.

13.2 Insurance

In Denmark, the Patient Insurance Association insures all Danish trial participants. Patient insurance will be ensured before initiating the trial in each of the participating countries if applicable.

13.3 Plan for publication, authorship and dissemination

13.3.1 Publication and authorship

The trial will be registered in the Clinical Trials (www.clinicaltrials.gov) and EudraCT (eudract.ema.europa.eu) registries. The final protocol will be published as a design and rationale paper including the detailed plan for analyses. Upon trial completion the main manuscript with trial results whether positive, negative or neutral will be submitted for a peer-

reviewed publication, to one of the major clinical journals. Furthermore, the results will be published at the HOT-ICU home page (www.cric.nu/hot-icu).

The listing of authors will be as follows: OL Schjørring will be the first author, TL Klitgaard will be second author (joint first authorship), A Perner the third, J Wetterslev the fourth, T Lange will be the fifth author and the next authors will be the national investigators as according to the number of included patients per country, then the trial statistician and the trial site investigators dependent on the number of included patients per site. BS Rasmussen will be the last and corresponding author, and the 'HOT-ICU trial investigators' will be written.

The SC will grant authorship depending on personal input according to the Vancouver definitions. If a trial site investigator is to gain authorship, the site has to include 50 patients or more. We aim for additional site authorships for each additional 50 patients included with the author names registered and listed in PubMed as minimum.
The DMSC and investigators not qualifying for authorship will be acknowledged with their names under the 'HOT-ICU Trial investigators' in an *appendix* to the final manuscript.
Funding sources will have no influence on the writing of the manuscript or the decision to publish.

13.4 Spin-off projects (if any)

Spin-off projects will be encouraged and conducted when approved by the SC. Presently no spin-off projects have been developed.

13.5 Intellectual property rights

The sponsor and primary investigator is BS Rasmussen. Therefore, no control of intellectual property rights is needed. The initiative for the HOT-ICU trial has been taken by BS Rasmussen and A Perner from CRIC and by doctors at multiple ICUs, none of whom have affiliations to institutions that may have economic interests in the trial results. Contracts between national investigators and Sponsor and between site investigators and Sponsor will be signed before conduct of the trial.

13.6 Trial timeline

2016 – May 2017: Governance approval applications, education of trials sites, other preparations

May 2017: First Danish patient enrolled

May 2019: Last patient enrolled

May 2020: Follow-up completed

14. References

1. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: A systematic review and meta-analysis. *Crit Care*. 2014;18(6):711.

2. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: A systematic review, meta-analysis, and meta-regression of cohort studies. *Crit Care Med*. 2015;43(7):1508-1519.

3. Gomersall CD, Joynt GM, Freebairn RC, Lai CK, Oh TE. Oxygen therapy for hypercapnic patients with chronic obstructive pulmonary disease and acute respiratory failure: A randomized, controlled pilot study. *Crit Care Med*. 2002;30(1):113-116.

4. Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med*. 2016;193(1):43-51.

5. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: The oxygen-ICU randomized clinical trial. *JAMA*. 2016.

6. Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative oxygen therapy in mechanically ventilated patients: A pilot before-and-after trial. *Crit Care Med*. 2014;42(6):1414-1422.

7. Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in critically ill patients: A before and after trial. *Crit Care Med*. 2016;44(3):554-563.

8. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care*. 2008;12(6):R156.

9. de Graaff AE, Dongelmans DA, Binnekade JM, de Jonge E. Clinicians' response to hyperoxia in ventilated patients in a dutch ICU depends on the level of FiO2. *Intensive Care Med*. 2011;37(1):46-51.

10. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med*. 2012;38(1):91-98.

11. Rachmale S, Li G, Wilson G, Malinchoc M, Gajic O. Practice of excessive F(IO(2)) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. *Respir Care*. 2012;57(11):1887-1893.

12. Panwar R, Capellier G, Schmutz N, et al. Current oxygenation practice in ventilated patients-an observational cohort study. *Anaesth Intensive Care*. 2013;41(4):505-514.

13. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: A prospective observational cohort study. *J Crit Care*. 2013;28(5):647-654.

14. Itagaki T, Nakano Y, Okuda N, et al. Hyperoxemia in mechanically ventilated, critically ill subjects: Incidence and related factors. *Respir Care*. 2015;60(3):335-340.

15. Zhang Z, Ji X. Quadratic function between arterial partial oxygen pressure and mortality risk in sepsis patients: An interaction with simplified acute physiology score. *Sci Rep*. 2016;6:35133.

16. Helmerhorst HJ, Arts DL, Schultz MJ, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med*. 2017;45(2):187-195.

17. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet*. 2010;376(9749):1339-1346.

18. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the united states. *Crit Care Med*. 2010;38(10):1947-1953.

19. Dowdy DW, Eid MP, Sedrakyan A, et al. Quality of life in adult survivors of critical illness: A systematic review of the literature. *Intensive Care Med*. 2005;31(5):611-620.

20. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: A systematic review of the literature. *Crit Care Med*. 2010;38(12):2386-2400.

21. Combes A, Costa MA, Trouillet JL, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med*. 2003;31(5):1373-1381.

22. Chelluri L, Im KA, Belle SH, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med*. 2004;32(1):61-69.

23. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.

24. Kratz A, Lewandrowski KB. Case records of the massachusetts general hospital. weekly clinicopathological exercises. normal reference laboratory values. *N Engl J Med*. 1998;339(15):1063-1072.

25. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Case records of the massachusetts general hospital. weekly clinicopathological exercises. laboratory reference values. *N Engl J Med*. 2004;351(15):1548-1563.

26. Crapo RO, Jensen RL, Hegewald M, Tashkin DP. Arterial blood gas reference values for sea level and an altitude of 1,400 meters. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1525-1531.

27. O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax*. 2008;63 Suppl 6:vi1-68.

28. Sjoberg F, Singer M. The medical use of oxygen: A time for critical reappraisal. *J Intern Med*. 2013;274(6):505-528.

29. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. the acute respiratory distress syndrome network. *N Engl J Med*. 2000;342(18):1301-1308.

30. 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.

31. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. *JAMA*. 2012;308(16):1651-1659.

32. Kilickaya O, Gajic O. Initial ventilator settings for critically ill patients. *Crit Care*. 2013;17(2):123.

33. 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.

34. Jackson RM. Pulmonary oxygen toxicity. *Chest*. 1985;88(6):900-905.

35. Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: Implications for the provision of non-invasive ventilation and oxygen administration. *Thorax*. 2000;55(7):550-554.

36. Budinger GR, Mutlu GM. Balancing the risks and benefits of oxygen therapy in critically III adults. *Chest*. 2013;143(4):1151-1162.

37. MacIntyre NR. Supporting oxygenation in acute respiratory failure. *Respir Care*. 2013;58(1):142-150.

38. Dahl RM, Gronlykke L, Haase N, et al. Variability in targeted arterial oxygenation levels in patients with severe sepsis or septic shock. *Acta Anaesthesiol Scand*. 2015;59(7):859-869.

39. Mao C, Wong DT, Slutsky AS, Kavanagh BP. A quantitative assessment of how canadian intensivists believe they utilize oxygen in the intensive care unit. *Crit Care Med*. 1999;27(12):2806-2811.

40. Eastwood GM, Reade MC, Peck L, Jones D, Bellomo R. Intensivists' opinion and self-reported practice of oxygen therapy. *Anaesth Intensive Care*. 2011;39(1):122-126.

41. Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. *Ann Intensive Care*. 2014;4:23-014-0023-y. eCollection 2014.

42. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: The haemoglobin-oxygen dissociation curve. *Breathe (Sheff)*. 2015;11(3):194-201.

43. Iscoe S, Beasley R, Fisher JA. Supplementary oxygen for nonhypoxemic patients: O2 much of a good thing? *Crit Care*. 2011;15(3):305.

44. Cornet AD, Kooter AJ, Peters MJ, Smulders YM. The potential harm of oxygen therapy in medical emergencies. *Crit Care*. 2013;17(2):313.

45. 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.

46. Turrens JF. Mitochondrial formation of reactive oxygen species. *J Physiol*. 2003;552(Pt 2):335-344.

47. Zaher TE, Miller EJ, Morrow DM, Javdan M, Mantell LL. Hyperoxia-induced signal transduction pathways in pulmonary epithelial cells. *Free Radic Biol Med*. 2007;42(7):897-908.

48. Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care*. 2013;58(1):123-141.

49. 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;19:284-015-0996-4.

50. Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. *J Appl Physiol (1985)*. 2003;95(6):2453-2461.

51. Bak Z, Sjoberg F, Rousseau A, Steinvall I, Janerot-Sjoberg B. Human cardiovascular dose-response to supplemental oxygen. *Acta Physiol (Oxf)*. 2007;191(1):15-24.

52. Rothen HU, Sporre B, Engberg G, Wegenius G, Hogman M, Hedenstierna G. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. *Anesthesiology*. 1995;82(4):832-842.

53. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Prevention of atelectasis during general anaesthesia. *Lancet*. 1995;345(8962):1387-1391.

54. Aboab J, Jonson B, Kouatchet A, Taille S, Niklason L, Brochard L. Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome. *Intensive Care Med*. 2006;32(12):1979-1986.

55. Martin DS, Grocott MP. Oxygen therapy in critical illness: Precise control of arterial oxygenation and permissive hypoxemia. *Crit Care Med*. 2013;41(2):423-432.

56. Gilbert-Kawai ET, Mitchell K, Martin D, Carlisle J, Grocott MP. Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients. *Cochrane Database Syst Rev*. 2014;5:CD009931.

57. ClinicalTrials.gov hyperoxia and hypertonic saline in septic shock (Hyper2S). https://clinicaltrials.gov/ct2/show/NCT01722422.

58. Sutherasan Y, Vargas M, Brunetti I, Pelosi P. Ventilatory targets after cardiac arrest. *Minerva Anestesiol*. 2015;81(1):39-51.

59. Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administration of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis*. 1980;122(5):747-754.

60. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne JP. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1980;122(2):191-199.

61. Sassoon CS, Hassell KT, Mahutte CK. Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1987;135(4):907-911.

62. Hanson CW,3rd, Marshall BE, Frasch HF, Marshall C. Causes of hypercarbia with oxygen therapy in patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1996;24(1):23-28.

63. Dick CR, Liu Z, Sassoon CS, Berry RB, Mahutte CK. O2-induced change in ventilation and ventilatory drive in COPD. *Am J Respir Crit Care Med*. 1997;155(2):609-614.

64. Scano G, Spinelli A, Duranti R, et al. Carbon dioxide responsiveness in COPD patients with and without chronic hypercapnia. *Eur Respir J*. 1995;8(1):78-85.

65. Robinson TD, Freiberg DB, Regnis JA, Young IH. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1524-1529.

66. Murphy R, Driscoll P, O'Driscoll R. Emergency oxygen therapy for the COPD patient. *Emerg Med J*. 2001;18(5):333-339.

67. Cameron L, Pilcher J, Weatherall M, Beasley R, Perrin K. The risk of serious adverse outcomes associated with hypoxaemia and hyperoxaemia in acute exacerbations of COPD. *Postgrad Med J*. 2012;88(1046):684-689.

68. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: Randomised controlled trial. *BMJ*. 2010;341:c5462.

69. Torres A, Reyes A, Roca J, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. *Am Rev Respir Dis*. 1989;140(5):1246-1250.

70. Crossley DJ, McGuire GP, Barrow PM, Houston PL. Influence of inspired oxygen concentration on deadspace, respiratory drive, and PaCO2 in intubated patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1997;25(9):1522-1526.

71. Santos C, Ferrer M, Roca J, Torres A, Hernandez C, Rodriguez-Roisin R. Pulmonary gas exchange response to oxygen breathing in acute lung injury. *Am J Respir Crit Care Med*. 2000;161(1):26-31.

72. Savi A, Gasparetto Maccari J, Frederico Tonietto T, et al. Influence of FIO2 on PaCO2 during noninvasive ventilation in patients with COPD. *Respir Care*. 2014;59(3):383-387.

73. Dunn WF, Nelson SB, Hubmayr RD. Oxygen-induced hypercarbia in obstructive pulmonary disease. *Am Rev Respir Dis*. 1991;144(3 Pt 1):526-530.

74. Rialp G, Raurich JM, Llompart-Pou JA, Ayestaran I. Role of respiratory drive in hyperoxia-induced hypercapnia in ready-to-wean subjects with COPD. *Respir Care*. 2015;60(3):328-334.

75. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *Br Med J*. 1976;1(6018):1121-1123.

76. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation*. 2015;131(24):2143-2150.

77. Nehme Z, Stub D, Bernard S, et al. Effect of supplemental oxygen exposure on myocardial injury in ST-elevation myocardial infarction. *Heart*. 2016.

78. Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. 2016;12:CD007160.

79. Khan AR, Abdulhak AB, Luni FK, et al. Oxygen administration does not influence the prognosis of acute myocardial infarction: A meta-analysis. *Am J Ther*. 2016.

80. Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Oxygen in the setting of acute myocardial infarction: Is it really a breath of fresh air? *J Cardiovasc Pharmacol Ther*. 2016;21(2):143-149.

81. Lægemiddelstyrelsen DMA. PRODUKTRESUMÈ for Medicinsk Oxygen "air liquide" 100%, medicinsk gas, kryogen. 2015.

82. BOC, A member of the Linde Group. Medical gas data sheet (MGDS)
compressed medical oxygen
essential safety information
summary of produc characteristics (SPC).
https://www.boconline.co.uk/internet.lg.lg.gbr/en/images/mgds-medical-oxygen-compressed410_55836.pdf?v=5.0. Updated 2014.

83. Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev*. 2015;6:CD008884.

84. DID. Dansk intensiv database, National årsrapport 2015/2016. *Regionernes Kliniske Kvalitetsudviklingsprogram*. 2016;December.

85. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41(5):833-845.

86. WMA decleration of helsinki - ethical principles for medical research involving human subjects. http://www.wma.net/en/30publications/10policies/b3/. Updated 2013.

87. European Medicines Agency. ICH harmonised tripartite guideline E6: Note for guidance on good clinical practice (PMP/ICH/135/95). *London*. 2002.

88. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.

89. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381-1391.

90. International Committee of Medical Journal Editors. Vancouver protocol uniform requirements for manuscripts submitted to biomedical journals. http://www.research.mq.edu.au/documents/policies/Vancouver.pdf2017.

91. International conference on harmonisation; guidance on statistical principles for clinical trials; availability--FDA. notice. *Fed Regist*. 1998;63(179):49583-49598.

92. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: The intention to treat principle and excluding patients from analysis. *BMJ*. 2002;325(7365):652-654.

93. The European Parliament and the Council of the European Union. DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 april 2001. *Official Journal of the European Communities*. 2001;121:34-44.

94. Gabriel SE, Normand SL. Getting the methods right--the foundation of patient-centered outcomes research. *N Engl J Med*. 2012;367(9):787-790.

95. Schmiemann G. The preliminary draft of the methodology report by the patient-centered outcomes research institute. *Z Evid Fortbild Qual Gesundhwes*. 2012;106(7):496-499.

96. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med*. 2012;31(4):328-340.

97. Lan K, DeMets D. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.

98. Mallinckrodt CH, Lin Q, Molenberghs M. A structured framework for assessing sensitivity to missing data assumptions in longitudinal clinical trials. *Pharm Stat*. 2013;12(1):1-6.

99. Little R. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc*. 1988;83:1198.

100. Schafer JL. Multiple imputation: A primer. *Stat Methods Med Res*. 1999;8(1):3-15.

101. Vickers AJ, Altman DG. Statistics notes: Missing outcomes in randomised trials. *BMJ*. 2013;346:f3438.

102. Qaseem A, Snow V, Shekelle P, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline from the american college of physicians. *Ann Intern Med*. 2007;147(9):633-638.

103. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues, fourth edition
WHO classification of tumours, volume 2 IARC WHO classification of tumours, no 2 unpublished, revised edition expected spring 2017. http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4002. Updated 20172017.

104. Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. on behalf of the working group on sepsis-related problems of the european society of intensive care medicine. *Intensive Care Med*. 1996;22(7):707-710.

105. Barbateskovic M, Schjørring OL, Jakobsen JC, et al. Higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation for adult intensive care patients (protocol). *Cochrane database systematic review*. 2017(4).

106. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *Eur Respir J*. 2014;44(4):1023-1041.

107. Tan HL, Wijeweera O. Oxygen in critical care. *Trends in Anaesthesia and Critical Care*. 2014;4:102-108.

108. SMITH G, LAWSON DA. Experimental coronary arterial occlusion: Effects of the administration of oxygen under pressure. *Scott Med J*. 1958;3(8):346-350.

109. Milone SD, Newton GE, Parker JD. Hemodynamic and biochemical effects of 100% oxygen breathing in humans. *Can J Physiol Pharmacol*. 1999;77(2):124-130.

110. McNulty PH, King N, Scott S, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol*. 2005;288(3):H1057-62.

111. McNulty PH, Robertson BJ, Tulli MA, et al. Effect of hyperoxia and vitamin C on coronary blood flow in patients with ischemic heart disease. *J Appl Physiol (1985)*. 2007;102(5):2040-2045.

112. Rousseau A, Bak Z, Janerot-Sjoberg B, Sjoberg F. Acute hyperoxaemia-induced effects on regional blood flow, oxygen consumption and central circulation in man. *Acta Physiol Scand*. 2005;183(3):231-240.

113. Kallstrom TJ, American Association for Respiratory Care (AARC). AARC clinical practice guideline: Oxygen therapy for adults in the acute care facility--2002 revision & update. *Respir Care*. 2002;47(6):717-720.

114. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165-228.

115. ANZCOR. Guideline 11.6.1 - target oxygen therapy in adult advanced life support. . 2016;January.

116. Jakobsen JC, Gluud C. The necessity of randomized clinical trials. *British Journal of Medicine & Medical Research*. 2013;3(4):1453-1468.

15. Appendixes

Appendix 1: Research Program Organisation

Appendix 2: Undesirable effects of oxygen

Appendix 3: Charter of the independent Data Monitoring and Safety Committee

Appendix 4: Definitions

Appendix 5: Translation of the Danish summary of product characteristics

Appendix 6: Informed consent in Denmark

Appendix 7: Timeline

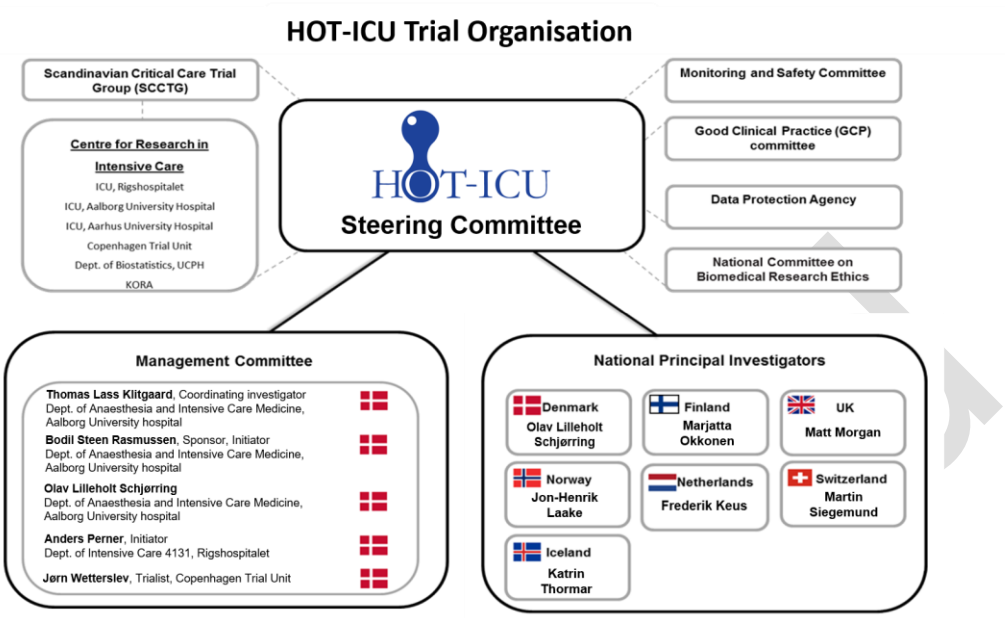
Appendix 8: SOFA Score

Appendix 9: Power estimation of secondary outcomes

Appendix 10: Trial sequential analysis

Appendix 11: International Committee of Medical Journal Editors (ICMJE) form for potential conflicts of interest

Appendix 1. Trial organisation



Appendix 2. Undesirable effects of oxygen

It is unknown how many patients that can be expected to experience adverse drug reactions. For all adverse reactions reported from post-marketing experience, it is not possible to apply any adverse reaction frequency.

Pleuritis, atelectasis and ARDS are listed as adverse reactions with low incidences; i.e. pleuritis and atelectasis in less than 1% of patients given oxygen therapy and ARDS in less than 0.01% of patient receiving oxygen therapy (see SPC for oxygen in *Appendix 5*). Pleuritis in not serious and can only be diagnosed in conscious patients.
As the presence of atelectasis is inevitable and ARDS is ubiquitous in critically ill patients admitted to the ICU with acute hypoxaemic respiratory failure, these conditions are as such indistinguishable from the adverse drug reactions of oxygen. The incidence of atelectasis and ARDS will be caught by the daily registrations of PaO_2 and FiO_2 and by the secondary effect parameter being days alive without the use of respiratory support in the 90-day period. A closer registration of atelectasis and ARDS would require daily CT-scans of the lungs which is far beyond the daily routine and would add additionally risk to the patients.

Appendix 3. Charter for the independent Data Monitoring and Safety Committee (DMSC)

ClinicalTrials.gov Identifier: NCT03174002
Research Ethical Committee no: N-20170015

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the SC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the HOT-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of patients, their management, improving adherence to the protocol-specified regimens and retention of patients, and the procedures for data management and quality control.
The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.
The DMSC is planned by protocol to meet physically in order to evaluate the planned interim analyses of the HOT-ICU trial. The interim analyses will be performed by an independent statistician, who can be the biostatistician sitting in the DMSC, selected by the members of the DMSC (to be announced). The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail in order to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of SAEs yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome

measures and SAEs according to the intervention groups. Further, the DMSC can request unblinding of the interventions if suggested by the data, see section 'closes sessions'. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the SC of the HOT-ICU trial. As fast as possible, and no later than 48 hours, the SC has the responsibility to inform all investigators of the trial ad all the sites including patients in the trial, about the recommendation of the DMSC and the SC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomised clinical trials.

DMSC Members

Jean-Francois Timsit, The Medical and Infectious Diseases Intensive Care Unit, Bichat Teaching Hospital, Paris Diderot University, France

Daniel De Backer, Department of Intensive Care, Erasme University Hospital, Brussels, Belgium

DMSC Biostatistician

Andreas Kryger Jensen, Section of Biostatistics, Department of Health, University of Copenhagen, Denmark

Conflicts of interest

DMSC members will fill in and sign a declaration of conflicts of interests see *appendix 13*. DMSC membership has been restricted to individuals free of conflicts of interests. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the HOT-ICU trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsors of the trial, with the contract research organisation

(CRO) for the trial (if any), or with sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.
The DMSC will be responsible for deciding whether those consulting agreements or financial interests materially impact their objectivity.
The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interests during the course of the trial should resign from the DMSC.
DMSC membership is to be for the duration of the clinical trial. If any members leave the DSC during the course of the trial, the SC will appoint the replacement(s).

Formal interim analyses meeting

One interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-day follow-up of 1464 (approximately 50 % of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group.
At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy result while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the

DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the SC.
Closed reports will include analysis of the primary outcome measure. In addition, analyses of the secondary outcome measures and SAEs will also be reported. These closed reports will be prepared by independent biostatistician being a member of the DMSC, with assistance from the trial data manager, in a manner that allow them to remain blinded.
The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.
The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the SC to continue, hold or terminate the trial.
Interim analyses will be conducted after patient no. 1464 has been followed for 90 days. The DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SAEs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function[97]. If an analysis of the interim data from 1464 patients fulfils the

LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial[91]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 20% RRR will not be an option as intervention effects less than 20% RRR of all-cause mortality may be clinically relevant as well.
This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.
The SC is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.
The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the protocol. For the two intervention groups, the DMSC will evaluate data on:

<u>The primary outcome measure</u>
Mortality 90 days after randomisation of each patient (“landmark mortality”).

<u>The secondary outcome measures</u>

- The occurrence of SAEs in the ICU defined as new episodes of shock and myocardial, cerebral or intestinal ischemia

The DMSC will be provided with these data from the coordinating centre and CTU as:
Number of patients randomised
Number of patients randomised per intervention group
Number of patients stratified per stratification variable per intervention group

Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

The DMSC will be provided with a file containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

Row 2 to N (where N-1 is the number of patients having entered the trial) each contains the data of one patient.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

1. Screening id: a number that uniquely identifies the patient
2. Rand code: the randomisation code (Group 0 or 1). The DMSC is not to be informed on what interventions the groups received
3. New episode of shock the ICU after randomisation (1 = one or more episodes; 0 = no episodes)
4. AMI: acute myocardial ischemia in the ICU (1 = one or more episodes, 0 = no episodes)
5. Stroke: cerebral ischemia in the ICU (1 = one or more episodes, 0 = no episodes)
6. Intestinal ischaemia in the ICU (1 = one or more episodes, 0 = no episodes)

Appendix 4. Definitions

Definition of stratification variables

Site: all participating intensive care units (ICUs) will be assigned a number identifying the department.

Chronic obstructive pulmonary disease (COPD) as defined by one of the following two criteria[102]:

- Conducted spirometry in stable phase that is diagnostic of COPD: A forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio less than 0.7 or less than the lower limit of normal AND an FEV_1 less than 80 percent of predicted AND flow limitations must be incompletely reversible after the administration of an inhaled bronchodilator.
- Anamnestic COPD AND daily use of inhaled beta2-adrenergic and/or anticholinergic bronchodilators and/or inhaled glucocorticoids including: albuterol, levalbuterol, salmeterol, formoterol, arformoterol, indacaterol, vilanterol, olodaterol, tiotropium, aclidinium, umeclidinium, glycopyrronium, budesonide and fluticasone.

Active haematological malignancy as any interventions within the last 6 months against any to the following[103]:

- Leukemia: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), B-cell prolymphocytic (B-PLL), large granular lymphocytic leukemia (LGL)
- Lymphoma: Hodgkin's lymphomas, Non-Hodgkin's lymphoma (e.g. small lymphocytic lymphoma (SLL), lymphoblastic lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), hairy cell leukemia (HCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), post-transplant lymphoproliferative disorder (PTLD), , Waldenström's macroglobulinemia, NK- og T-cell lymphomas).
- Multiple myeloma/plasma cell myeloma, solitary plasmacytoma
- Myelodysplastic syndromes

- Myeloproliferative neoplasms (MPN) (e.g. chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, primary myelofibrosis (PMF), myeloproliferative neoplasm, unclassifiable, Mast cell diseases
- Other (rare) malignant lymphoid and myeloid diseases
- Benign haematological diseases: aplastic anaemia, autoimmune haemolytic anaemia

Definition of inclusion criteria

Acute admission to the ICU: a non-planned admission. It does not include planned recovery after surgery or similar planned admissions. ICU admission does not include admissions to semi-intensive care, intermediate care or similar high-dependency beds.

Age: the age of the patient in whole years at the time of randomisation. The age will be calculated from date of birth.

Supplementary oxygen criterion: one of the following

- A flow of oxygen of at least 10 L per minute in an open system irrespective of any flow of atmospheric air, including high-flow systems
- An FiO_2 of at least 0.50 in a closed system being invasive or non-invasive (mask or helmet) ventilation or a CPAP system (mask or helmet)

Expected duration of supplemental oxygen for at least 24 hours in the ICU: the treating clinician estimates that the patient will need supplementary oxygen for more than 24 hours AND remain admitted to the ICU for 24 hours. When in doubt of this forecast the patient should be enrolled.

Arterial line criterion: A functioning catheter for the sampling of arterial blood must be in place at the time of enrollment.

Definition of exclusion criteria

Not possible to randomise the patient within twelve hours of the present ICU admission: defined as 12 full hours from the time of the present ICU admission; if the patient is transferred from another ICU, the 12 hours will count from the time of the admission to this preceding ICU.

Chronic mechanical ventilation: invasive mechanical ventilation, continuous non-invasive ventilation or continuous mask-CPAP in an institution or at home. Nocturnal CPAP or non-invasive ventilation due to sleep apnea and/or obesity hypoventilation syndrome is *not* regarded as chronic mechanical ventilation.

Use of supplementary oxygen at home: prescribed supplementary oxygen given through nasal cannula, mask or tracheostomy on a regular daily basis independent whether it is continuously, in daytime or nocturnal.

Previous treatment with bleomycin: any history of bleomycin treatment (e.g. for testicular, ovarian, cervical cancer or haematological malignancy) documented in the patient charts.

Organ transplant: any kind of solid organ transplant planned, or performed during current hospitalisation.

Withdrawal from active therapy or brain death deemed imminent: clinicians or investigators judge that withdrawal from active therapy or brain death is likely within a few hours.

Pregnancy: Confirmed by positive urine human gonadotropin (hCG) or plasma-hCG.

Carbon monoxide poisoning: carbon monoxide poising confirmed during current critical illness by an arterial or venous blood carboxyhaemoglobin (COHb) > 3 percent for non-smokers and > 10 percent for active smokers during current hospitalisation.

Cyanide poisoning: suspected cyanide poisoning as judged by the clinicians during current hospitalisation and documented in the patient charts.

Methaemoglobinaemia: methaemoglobinaemia with a confirmed arterial or venous blood methaemoglobin > 8 % during current hospital admission.

Paraquat poisoning: any anamnesis of and/or suspected paraquat (pesticide) poisoning as judged by the clinicians during current hospitalisation and documented in the patient charts.

Sickle cell disease: any history of sickle cell disorder documented in patient charts and/or confirmed by the presence of haemoglobin S (HbS) in an arterial or a venous blood sample.

Any condition expected to involve the use of HBO: e.g. necrotising soft tissue infection in sites using HBO for this condition.

Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain the necessary consent before inclusion of the patient according to the national regulations.

Patients previously enrolled in the HOT-ICU trial: Patients enrolled in the HOT-ICU trial in a previous ICU admission. If it is still within the follow-up period of 90 days since randomisation, the patient should continue in the allocated intervention group.

Definition of baseline variables

Sex: the genotypic sex of the patient

Age: defined in inclusion criteria

Patient height: In centimetres, if lower extremities are bilaterally amputated, the estimated original height should be used

Date of admission to hospital: the date of admission to the first hospital the patient was admitted to during the current hospitalisation

Date and time of admission to ICU: the time of admission to the first ICU the patient was admitted to during the current hospitalisation

Elective surgery: surgery scheduled 24 hours or earlier in advance

Emergency surgery: surgery scheduled ≤ 24 hours in advance

Medical admission: all admission that are not originating from the operating or recovery room will be considered medical irrespective of any surgery done during current hospital admission.

Many of these admissions will be due to medical complications secondary to surgery (e.g. pneumonia, atelectasis, thromboembolic events)

Respiratory support: invasive ventilation, non-invasive ventilation or non-intermittent CPAP at the time of randomisation (as defined under *Definition of daily variables*)

If receiving respiratory support, registration of TV, PEEP and P-peak, or CPAP pressure at the time of randomisation

PaO_2, SaO_2 and serum-lactate in the *last* arterial blood gas sample conducted within twelve hours *before* randomisation. Corresponding FiO_2: If receiving oxygen through an open system (as defined under *Definition of inclusion criteria*) FiO_2 will be estimated from conversion tables depicting type of open system, flow and, oxygen concentration

Acute co-morbidities leading to or occurring during the current hospitalisation defined as follows:

- Pneumonia: as defined by the clinician and noted in the patient files
- Shock: defined as the use of vasopressors or inotropes (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosemindan) to maintain a mean arterial pressure > 65 mmHg after initial fluid therapy AND lactate > 2.0 mmol/L
- Multiple trauma: acute accident resulting in injuries to tissue at two anatomical sites or more
- Stroke: verified cerebral bleeding, ischemia or embolism on CT- or MRI-scan or acute ischemia or embolism diagnosed by a neurologist
- Myocardial infarction: verified by ECG findings, significant rise in coronary biomarkers and/or percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during current hospitalisation
- Cardiac arrest before randomisation: Cardiac arrest with initiated cardiopulmonary resuscitation leading to or happened during current ICU admission

- Intestinal ischaemia: onset of gastric, mesenteric or colonic ischaemia verified though exploratory or diagnostic abdominal surgery, gastroscopy or colonoscopy, or findings of intestinal ischaemia on CT- or MR angiography during current hospitalisation.
- Traumatic brain injury as verified by fresh lesions on CT- or MR-scan
- ARDS: defined as bilateral chest infiltrates on x-ray and a PaO_2/FiO_2 ratio below 40 kPa (300 mmHg) in mechanically ventilated patients with PEEP ≥ 5 cmH_2O or CPAP ≥ 5 cm H_2O. The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload
- Acute renal failure: defined as plasma creatinine of 170 micromol/L or above (renal SOFA score 2) in the 24 hours prior to randomisation and normal plasma creatinine before hospital admission (documented or estimated)

- Chronic comorbidities must have been present in the past medical history prior to hospital admission and the events leading to this and are defined as follows:
- History of ischaemic heart disease as any of the following
    - Myocardial infarction: ST-elevation myocardial infarction, non-ST elevation myocardial infarction as defined by significant rise in coronary biomarkers.
    - Previous coronary intervention: PCI or CABG.
    - Previous stable or unstable angina pectoris: stable or unstable angina pectoris or use of nitrates indicating this.
- Chronic heart failure: Diagnosed with chronic heart failure defined as left ventricular ejection fraction ≤ 40% OR chronic heart failure with preserved left ventricular ejection fraction
- Active metastatic cancer: any metastases from a malignant non-haematological neoplasm, that is not is not considered eradicated at present. Complete radiological regression through oncological treatment is *not* considered eradication.

The Sequential Organ Failure Assessment (SOFA) Score[104] (*appendix* 10) will be calculated from raw physiology and treatment data from the 24 hours prior to randomisation. The respiratory score will however be calculated at the time of randomisation. The SOFA Score consists of weightings for six organ systems to give a total score ranging from 0 to 24, with higher scores indicating a greater degree of organ failure.

Definition of daily variables

Respiratory support on this day: Invasive mechanical ventilation defined as any positive airway pressure applied through an endotracheal tube or a tracheostomy tube; Non-invasive mechanical ventilation, including CPAP is defined as positive airway pressure applied through a mask or a helmet. Intermittent CPAP or non-invasive ventilation should NOT be counted as respiratory support.

Arterial blood gases and respiratory parameters: Registration of the highest and lowest PaO_2 values within every 12 hours with concomitant SaO_2 and FiO_2 measures.

Tidal volume, PEEP and P-peak at 08:00h if invasive mechanical ventilation is provided at this time point, CPAP or EPAP level at 08:00h if non-invasive mechanical ventilation or mask CPAP is provided at this time point.

Lactate: highest lactate every 24 hours.

Circulatory support: continuous infusion of vasopressor or inotrope (norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamin, milirinone or levosemindan).

Renal replacement therapy: any form of renal replacement therapy on this day. In patients receiving intermittent renal replacement therapy days between treatments are included.

Myocardial ischemia: ST-elevation myocardial infarction, non-ST elevation myocardial infarction or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) AND receiving treatment as a consequence of this: reperfusion strategies (PCI/thrombolysis) or initiation/increased antithrombotic treatment on this day.

Cerebral ischemic stroke: onset of neurological symptoms on this day and verified ischaemia on CT- or MR-scan.

Intestinal ischaemia: onset of gastric, mesenteric or colonic ischaemia on this day and verified though exploratory or diagnostic abdominal surgery, gastroscopy or colonoscopy, or findings of intestinal ischaemia on CT- or MR angiography.

Units of red blood cells: cumulated number of units of red blood cells transfusion during the day.

Definitions of outcome measures

Primary outcome:

90-day mortality: death from any cause within 90 days following the day of randomisation

Secondary outcomes:

Proportion of patients with one of more of the following SAE: acute myocardial ischaemia, ischemic stroke, intestinal ischemia or new episode of shock. The events are defined in *Definitions of daily variables*.

1-year mortality: landmark mortality 1 year post-randomisation

Days alive without use of respiratory support, circulatory support or renal replacement therapy in the 90-day period: defined as the percentage of days alive without respiratory support, circulatory support and renal replacement therapy (as defined in daily collected variables) in 90 days after randomisation

Day alive out of the hospital in the 90-day period

EQ-5D-5L and EQ-VAS score

RBANS score (selected sites)

Appendix 5. Translation of the Danish summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

for

Medicinal Oxygen 'Air Liquide' 100 %, medicinal gas, cryogenic

0. D.SP.NR.
25715

1. NAME OF THE MEDICINAL PRODUCT
Medicinal Oxygen "Air Liquide" 100 %

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Oxygen 100 %.

3. PHARMACEUTICAL FORM
Medicinal gas, cryogenic.
Colourless, odourless and tasteless

4. CLINICAL PARTICULARS

4.0 Therapeutic indications

Oxygen therapy
- Treatment or prevention of acute and chronic hypoxia irrespective of cause.
- Part of the fresh gas flow in anaesthesia or intensive care treatment.
- Propellant gas in the treatment with a nebulizer
- Treatment of an acute attack of cluster headache

Hyperbaric oxygen therapy
Treatment of decompression sickness, air and gas embolism from other causes and carbon monoxide poisoning.
Treatment of patients who have been exposed to carbon monoxide are indicated especially in pregnant women or patients who are or have been unconscious or who have shown neurological symptoms and/or cardiovascular effects or severe acidosis regardless of the measured COHb value.

Additionally, it can be used in the treatment of severe osteoradionecrosis and clostridial myonecrosis (gas gangrene).

4.1 Posology and method of administration

Dosage

Oxygen therapy
The purpose of the therapy is to ensure that the oxygen partial pressure in arterial blood (PaO_2) does not fall below 8.0 kPa (60 mmHg) or the oxygen saturation of haemoglobin in arterial blood does not fall below 90% by adjusting the oxygen fraction in the inhaled air (FiO_2)

The dose (FiO_2) should be adapted to the individual needs of the patient, taking the risk of oxygen toxicity into account. In order to obtain the expected results of the treatment, it is generally recommended to use the lowest dose (FiO2) as possible. In case of pronounced hypoxia, fractions of oxygen that may induce a risk of oxygen toxicity can be indicated (see section. 4.9).

The treatment must be continuously evaluated and the effect measured by means of PaO_2 or arterial oxygen saturation (SpO_2).

In short-term oxygen therapy, the oxygen concentration – the fraction in the inhaled gas mixture (FiO_2) (avoid> 0.6 = 60% O_2 in the inhaled gas mixture) - must be kept so that with or without a positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) can reach an arterial oxygen pressure (PaO_2)> 8 kPa.

Short-term oxygen therapy must be monitored/observed by repeated measures of the arterial oxygen pressure (PaO_2) or pulse oximetry, which gives a numerical value for haemoglobin oxygen saturation (SpO_2). They are, however, only indirect measurements of the oxygen saturation in tissues. The effect of the therapy must also be clinical evaluated.

In an acute situation, the usual dose for adults in treatment or prevention of *acute oxygen deficiency* is 3-4 liters per minute when using nasal cannula and 5-15 liters per minute when using a mask.

In long-term therapy the need for extra oxygen is controlled by the result of the measurements of arterial blood gas. For adjusting oxygen therapy in patients with hypercapnia, blood gases should be monitored in order to avoid a significant increased carbon dioxide tension in arterial blood.

If oxygen is mixed with other gases, the oxygen fraction in the inhaled gas mixture (FiO_2) must not be lower than 21% and may be up to 100%.

For treatment of cluster headache, oxygen is delivered by a facemask, in a non-rebreathing system. Oxygen therapy should be instituted early after onset of the attack and should last for about 15 minutes or until the pain has disappeared. Usually, a flow of 7-10 litres/min is sufficient but a flow rate up to 15 litres/min. may be required in some patients to achieve an effect. Oxygen should be discontinued if no effect occurs within 15-20 minutes.

Hyperbaric oxygen therapy
Hyperbaric oxygen therapy (HBO) is to administer 100% oxygen at pressures over 1.4 times the atmospheric pressure at sea level (1 atmosphere = 101.3 kPa = 760 mmHg). For safety

reasons the pressure in HBO should not exceed 3.0 atmosphere. Each treatment session at 2-3 atm usually lasts between 60 minutes and 4-6 hours depending on the indication. If necessary, the sessions can be repeated 2-3 times a day depending on the indication and the clinical condition. Repeated treatments are often necessary when it comes to treatment of soft tissue infections and ischemic ulcers that do not respond to conventional therapy. HBO should be given by personnel who are competent to do so. Increasing and reducing the pressure must be conducted slowly in order to avoid the risk of pressure damage (barotrauma).

Pediatric population
Neonates must be closely monitored during treatment. The lowest effective concentrations should be kept to ensure adequate oxygenation.

Administration

Oxygen therapy
Oxygen is administered via the inspired air.

Oxygen can also be supplied through a so-called 'oxygenator' directly into the blood e.g. in the case of cardiac surgery with a heart–lung machine and in other conditions that require extracorporeal circulation.

Oxygen is administered by means of equipment intended for this purpose. With this equipment, the oxygen is supplied to the inspired air and upon expiration the exhaled gas with any excess of oxygen passes from the patient and is mixed with the surrounding air (non-rebreathing system).
For treatment of cluster headache, oxygen is delivered by a facemask in a non re-breathing system. For anaesthesia, special equipment is often used in which the exhaled gas recirculates and can in part be re-inhaled (circular system with rebreathing). There are a large number of devices intended for oxygen administration.

Low-flow system:
The simplest system, which mixes oxygen with the inhaled air, e.g. a system in which the oxygen is dosed via a simple rotameter and a nasal cannula or facemask.

High-flow system:
A system intended to supply a gas mixture corresponding to the patient's breath. This system is intended to produce a fixed oxygen concentration that is not affected or diluted by the surrounding air, e.g. a Venturi mask with a constant oxygen flow in order to deliver a fixed oxygen concentration in the inhaled air.

Hyperbaric oxygen therapy
Hyperbaric oxygen therapy (HBO) is administered in a specially constructed pressure chamber intended for hyperbaric oxygen therapy in which pressures up to 3 atmospheres (atm) can be maintained. HBO can also be given using a close-fitting facial mask, a hood covering the head or through a tracheal tube.

4.2 Contra indications

There are no absolute contraindications for oxygen therapy.

4.3 Special warnings and precautions for use

High oxygen concentrations should be given for the shortest possible time required to achieve the desired result and must be monitored with repeated checks of arterial gas pressure (PaO2) or haemoglobin oxygen saturation (SpO2) and the inhaled oxygen concentration (FiO2).

In the literature evidence is found that the risk of oxygen toxicity can be considered minimal if the following recommendations are followed:

- Oxygen concentrations up to 100 % (FiO_2 1.0) should not be given for more than 6 hours
- Oxygen concentrations above 60-70 % (FiO_2 0.6-0.7) should not be given for more than 24 hours
- Oxygen concentrations > 40 % (FiO_2 > 0.4) can possibly cause damage after 2 days

These recommendations do not apply in neonates because retrolental fibroplasia occurs at a much lower FiO_2 level. Therefore, the aim must be to keep the concentration at the absolute lowest to ensure appropriate oxygenation.

In any use of oxygen caution should be taken in regards to the high-risk of spontanteous combustion. This risk increases at procedures involving diathermy, defibrillation and electro conversion.

With high concentrations of oxygen in the inspired air/gas, the concentration/pressure of nitrogen is reduced. As a result, the concentration of nitrogen in tissues and lungs (the alveoli) falls. If oxygen is taken up from the alveoli into the blood more rapidly than it is supplied through ventilation alveolar collapse may occur (development of atelectasis). The development of atelectatic sections of the lungs lead to a risk of poorer arterial blood oxygen saturation, due to lack of gas exchange in the atelectatic sections of the lungs in spite of good perfusion. The ventilation/perfusion ratio worsens, leading to intrapulmonary shunt.

High concentrations of oxygen in vulnerable patients, with reduced sensitivity to the carbon dioxide tension in arterial blood can cause carbon dioxide retention, which in extreme cases can lead to carbon dioxide narcosis.

In hyperbaric oxygen therapy, the pressure should be increased and reduced slowly in order to avoid the risk of pressure damage (barotrauma).
Hyperbaric oxygen therapy should be used with caution during pregnancy and in fertile women (see section. 4.6).

HBO should be used with caution in patients with pneumothorax.

4.4 Interaction with other drugs and other sorts of interaction

The pulmonary toxicity associated with the use of drugs such as bleomycin, amiodarone and nitrofurantoin and similar antibiotics, can be aggravated by inhalation of high oxygen concentrations.

4.5 Pregnancy and lactation

Oxygen may be used during pregnancy and lactation.
Hyperbaric oxygen therapy should be used with caution during pregnancy and in fertile women due to the potential risk of oxidative stress induced damage to the fetus. In severe carbon monoxide poisoning the advantage of using hyperbaric oxygen therapy seems to outweigh the risk. However, the use should be evaluated individually for each patient.

4.6 Effects on ability to drive or operate machines

No labelling.
Not relevant.

4.7 Adverse reactions

	Uncommon (≥ 1/1.000 to < 1/100)	**Rare (≥ 1/10.000 to < 1/1.000)**	**Very rare (< 1/10.000)**
The nervous system			Hyperbaric oxygen therapy Anxiety; confusion; loss of consciousness; unspecified epilepsy
Eyes		Retrolental fibroplasia in neonates who have been exposed to high concentrations of oxygen	
Ears and labyrinth	Hyperbaric oxygen Sensation of pressure in the middle ear; rupture of eardrum		
Airways, thorax and mediastinum	Atelectasis; pleuritis		Acute Respiratory Distress syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Physicians and healthcare professionals are asked to report any suspected adverse reactions to:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Web: www.meldenbivirkning.dk
E-mail: dkma@dkma.dk

4.8 Overdose

Overdose of oxygen does not occur outside the intensive care unit and the risk is higher with hyperbaric oxygen therapy.

In case of oxygen intoxication (symptoms of oxygen toxicity), the oxygen treatment must be reduced or if possible stopped and symptomatic treatment should be initiated in order to maintain vital functions (e.g. artificial ventilation/assisted ventilation should be started if the patient shows signs of respiratory depression).

4.9 Delivery

GH

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification: ATC code: V03AN01. All other therapeutic products - medicinal gases, oxygen.

5.1 Pharmacodynamic properties

Oxygen constitutes approx. 21 % of the air we breathe. Oxygen is vital for humans and must be supplied continually to all tissues in order to maintain the cellular energy production. Oxygen in inhaled air is transported through the airways into the lungs. As a result of the difference in partial pressures a gas exchange in the alveoli of the lungs from the inhaled air/gas mixture to the blood in the capillaries occurs. Oxygen is transported further into the systemic circulation, mainly bound to haemoglobin, to the capillaries in the bodily tissues. Oxygen is transported through the pressure gradient out into the various cells. Its goal being the mitochondria in the individual cells, in which the oxygen takes part in an enzymatic chain reaction creating energy. By increasing the oxygen fraction in the inhaled air/gas mixture, the partial pressure gradient that controls the transport of oxygen to the cells increases.

When oxygen is supplied at a pressures higher than the atmospheric pressure (HBO), the amount of oxygen carried in the blood to the peripheral tissues increases significantly. Intermittent hyperbaric oxygen therapy even generate oxygen transport to oedematous tissue and tissue with inadequate perfusion and may in this way maintain cellular energy production and function. In accordance with Boyle's law, HBO reduces the volume of air bubbles in tissue in relation to the pressure at which it is given.

HBO counteracts the growth of anaerobic bacteria.

5.2 Pharmacokinetic properties

Inhaled oxygen is absorbed by a pressure-dependent gas exchange between alveolar gas and the capillary blood that passes the alveoli.

Oxygen is transported by the systemic circulation to all tissues in the body, mostly bound to haemoglobin (21 ml/100 mg blood). Only a very small proportion of oxygen is freely dissolved in the plasma (0.3 ml/100 ml blood). On passage through tissue, partial pressure-dependent transport of the oxygen to the individual cells takes place. Oxygen is a vital component in the

intermediate metabolism of the cell. Oxygen is important to the cell's metabolism primarily in order to create energy through the aerobic ATP production in the mitochondria.

Oxygen accelerates the release of carbon monoxide that is bound to haemoglobin, myoglobin and other iron-containing proteins, and thus counteracts the negative obstructing effects caused by the binding of carbon monoxide to iron.

Hyperbaric oxygen therapy further accelerates the release of carbon monoxide, as compared with 100 % oxygen under normal pressure.

Virtually all oxygen that is absorbed in the body is exhaled as carbon dioxide formed in the intermediate metabolism.

5.3 Preclinical safety data

Animal studies have shown that long-term continuous inhalation of pure oxygen may elicit harmful effects. Tissue damage can be induced in the lungs, the eyes and the central nervous system. A profound variability of the time to occurrence of pathological changes in different species and in animals of the same species exists.
Hyperbaric oxygen therapy during gestation in mice, rats, hamsters and rabbits led to increased resorption and foetal abnormalities and reduced birth weight.

6. PHARMACEUTICAL PARTICULARS

6.0 List of excipients
None.

6.1 Incompatibilities
Not relevant.

6.2 Shelf life

Cryogenic vessels < 30 litres: 1 month
Cyrogenic vessels ≥ 30 litres: 45 days

6.3 Special precautions for storage

Storage instructions relating to the medicinal product

This medicinal product does not require any special storage instructions in regards to temperature other than those that apply for gas containers and gas under pressure (see below). Store cryogenic vessels in a locked room reserved medicinal gases (does not apply in private homes).

Storage instructions relating to gas containers and gases under pressure

Contact with combustible material may cause fire.
Keep away from combustible material.
No smoking.
Risk of explosion upon contact with oil and grease.
Must not be exposed to strong heat. Move to a safe place in the event of fire.
Handle carefully. Do not drop or bump.
Keep clean and dry. Store in a ventilated place reserved medicinal gases.
Store and transport upright with valves closed.

6.4 Nature and contents of container

All container closure systems are vacuum-insulated containers made of stainless steel and aluminium intended for storing low temperature condensed gases at approximately -180ºC.
The following sizes are used:

Containers:
Storage tank for cryogenic gas, portable and equipped with a dosing device for regulating the gas flow to the patient: 10 liters - 36 litres.
Storage tank for cryogenic gas, portable: 228 litres – 627 litres.

All pack sizes may not necessarily be marketed.
The table below gives the approximately volume of gas in kg.

Vessel size in litre	10	12	15	20	21	30	31	36	37	40
kg gas	11.4	13.7	17.1	22.8	24.0	34.2	35.4	41.1	42.2	45.6

Vessel size in litre	228	450	600	627
kg gas	260	513	685	715

6.5 Special precautions for disposal and other handling

Instructions for use and handling

Storage tank for cryogenic gas, portable

In general

Medicinal gases must only be used for medicinal purposes.

Different gas types and gas qualities must be separated from each other.

Full and empty containers should be stored separately.

Never use oil or grease as lubricant in screw threads, even if the vessel valve is stiff or if the regulator is difficult to connect.

Handle valves and matching devices with clean and grease-free (hand cream, etc.) hands.

Use only standard equipment that is intended for medicinal oxygen.

Preparation for use

Use only regulators intended for medicinal oxygen.

Check that the automatic coupling or regulator is clean and that the gaskets are in good condition. Never use a tool on a stuck pressure/flow regulator which is intended to be connected manually, as this may damage the coupling.

Open the vessel valve slowly – at least half a turn.

Check for leakage in accordance with the instruction that accompanies the regulator.

In the event of leakage, close the valve and uncouple the regulator. Label defective vessels, put them aside and return them to the supplier.

Using the gas vessel

Smoking and open flames are absolutely prohibited in rooms where oxygen therapy is being carried out.

Close down the equipment in the event of fire or if it is not being used.

Carry to safety in the event of fire.

Larger gas cylinders must be transported by means of a suitable type of trolley.

Take special care that connected devices are not inadvertently loosened.

When the vessel is empty, the gas flow will fall. Close the vessel outlet valve and disconnect after depressurising.

7. MARKETING AUTHORISATION HOLDER

AIR LIQUIDE Santé INTERNATIONAL

75 quai d'Orsay

75007 Paris

France

Representative

AIR LIQUIDE GAS AB

Lundevägen 151

S-212 24 Malmø

Sweden

8. MARKETING AUTHORISATION NUMBER(S)

42860

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 18th 2010

10. DATE OF REVISION OF THE TEXT

December 7th 2015

Appendix 6. Informed consent, Denmark

In Denmark temporarily incompetent patients will be enrolled after informed consent from one physician, who is independent of the trial (first trial guardian). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second physician (second trial guardian). The second trial guardian must be different from the first trial guardian, but also independent of the trial. Patients, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

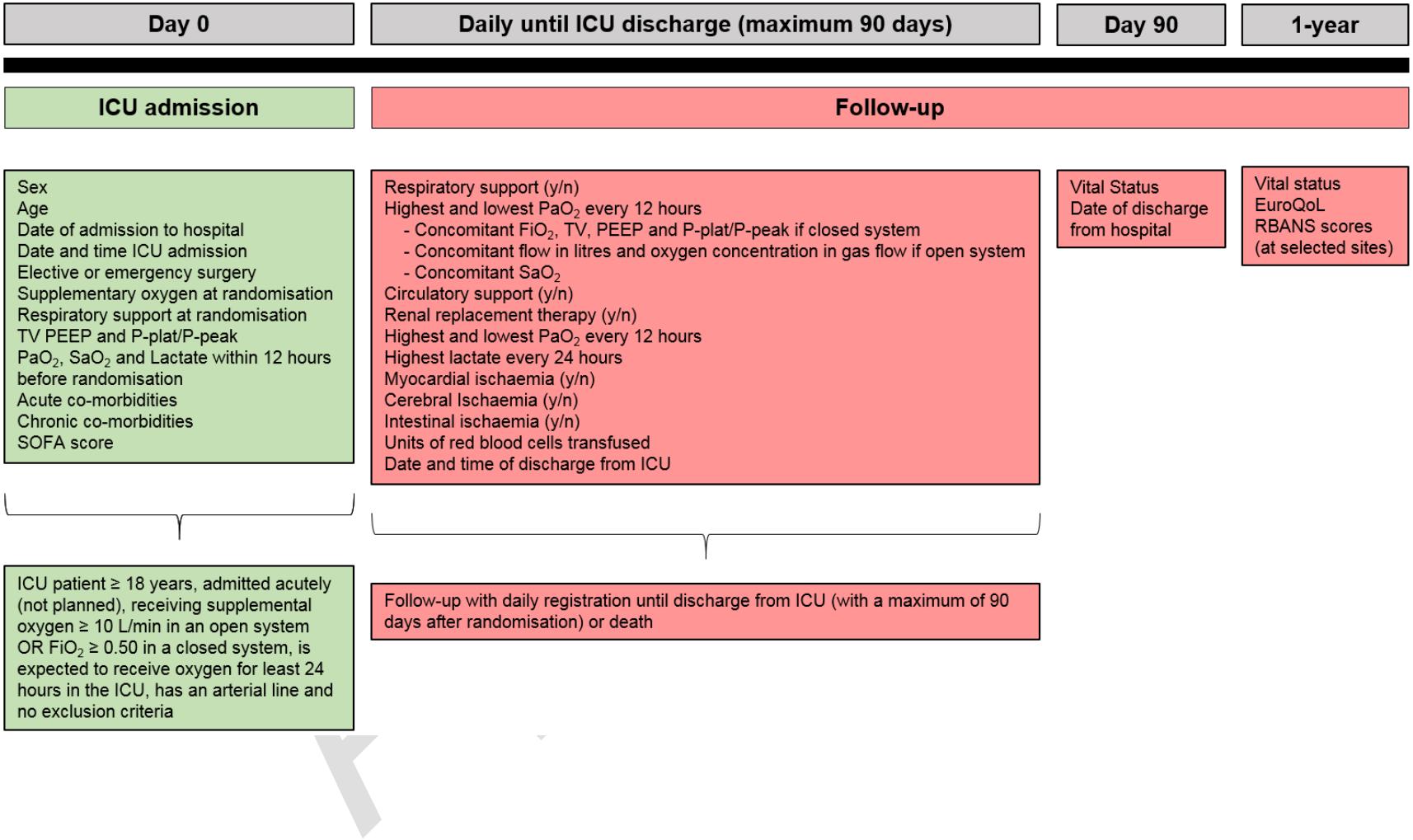
Lack of informed consent from the patient's next of kin
If information about the patient's next of kin is not available after inclusion the investigator will seek information from e.g. the patient's general practitioner, the police, nursing homes etc. In these situations it may take 1-2 weeks to conclude that no next of kin can be identified. If no one is identified and the patient remains incompetent the trial intervention will be discontinued. All initiatives to identify the patient's next of kin will be documented in patient files, logs or similar.

Lack of informed consent from the patient's next of kin and the patient deceases
If the patient deceases before informed consent has been obtained (due to rapid progression of critical illness or because the patient's next of kin is not yet identified) and the patient has been correctly included in the trial, collected data will be kept for analysis.

Deviation from the standard informed consent
According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge

about the specific patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

Appendix 7. Timeline



Appendix 8. SOFA score[104]

	0	1	2	3	4
Respiration					
PaO_2/FiO_2 (mmHg)	≥ 400	< 400	< 300*	< 200†	< 100†
(KPa)	≥ 53	< 53	< 40*	< 27†	< 13†
Coagulation					
Platelets (x 10^3/mm3)	≥ 150	101-150	51-100	21-50	≤ 20
Liver					
Bilirubin					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
(µmol/l)	< 20	20-32	33-101	102-204	> 204
Cardiovascular					
Hypotension* (MAP)	≥ 70	< 70	Dopamine ≤ 5☼ **OR** Dobutamine (any dose) **OR** Milrirone (any dose) **OR** Levosimendan (any dose) **OR**	Dopamine ≥ 5☼ **OR** Norepinephrine ≤ 0.1☼ **OR** Adrenaline ≤ 0.1☼ **OR** Vasopressin (any dose) **OR** Phenylephrine (any dose) **OR**	Dopamine > 15☼ **OR** Norepinephrine > 0.1☼ **OR** Adrenaline > 0.1☼
CNS					
Glascow coma scale score	15	13-14	10-12	6-9	< 6
Renal					
Creatinine					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(µmol/l)	< 110	110-170	171-299	300-440	>440
OR					
Urine output				<500 ml/day	<200 ml/day

* without respiratory support
† with respiratory support
☼Adrenergic agents administered for at least one hour (doses given are in µg/kg/min).

Appendix 9. Power estimation of secondary outcomes

The secondary outcomes are calculated based on data from our two RCTs[88,89].

Number of patients with one or more ischaemic events or new episodes of shock (SAEs) in the ICUs after randomization

The power will be 80% to detect or reject an increase in the fraction of SAE from 9 % to 12 % (a 33 % relative risk increase) or a decrease from 9 % to 6.3 % (a 30 % relative risk reduction).

The mean percentage of days calculated as the number of days alive without the use of respiratory support, renal replacement therapy or circulatory support divided by the number of days alive during the 90-days period

The power will be 80 % to detect or reject a difference of 5 % points.

Days alive and out of hospital in the 90-day period

The power will be 80% to detect of reject a difference of 5 % points.

Mortality 1-year after randomisation

One year mortality assuming an absolute increase in mortality from 90 days to 365 days of 5 % and a 90 days mortality of 25 % in the control group will provide the HOT-ICU trial with a 80 % power to detect or reject a reduction in mortality from 30 % to 25.4 % (a 15.4 % relative risk reduction) and an increase in mortality from 30 % to 34.8 % (a 19.3 % relative risk increase).

Appendix 10. Trial sequential analysis of all-cause mortality

Effects of higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation in intensive care patients (ACE350). A preliminary summary of the systematic review results[105].

ICU patients often develop hypoxaemia (PaO_2 below 60 mmHg or an SaO2 below 90%[27], a clinical manifestation of inadequate gas exchange in the lungs[106]. In order to correct or prevent the hypoxaemic condition, patients admitted to the ICU often receive supplemental oxygen (defined as FiO_2 above 21%) via mechanical ventilation or oxygen support.
Several beneficial effects of supplemental oxygen have been proposed and include maintenance of delivery of oxygen to tissues, prevention of organ dysfunction followed by anoxic injury; an increase in the right-sided heart function as a reaction of pulmonary arterial vasodilation; induction of antioxidant enzymes, anti-inflammatory proteins, anti-inflammatory cytokines, and certain growth factors; reduced postoperative infections; neutrophil activation and markers of cerebral tissue breakdown; anti-apoptotic effects in brain and myocardium; normalisation of cerebral extracellular homeostasis; and stabilisation of the blood-brain barrier[36,107]. Inhalation of oxygen may eliminate hypoxaemia[27]. Furthermore, increasing the arterial oxygen tension has been shown to reduce the incidence of arrhythmias in animals after coronary artery ligation[108].
In contrast, high inspiratory oxygen concentrations have been associated with adverse outcomes in emergency medical conditions, including exacerbation of COPD[68]; resuscitation after cardiac arrest[1,2]; myocardial infarction[76]; stroke[1,2] and traumatic brain injury[1]. Studies have shown that administering supplemental oxygen to patients with cardiac diseases significantly increase coronary resistance and decrease coronary blood flow[109-111]. Oxidative reduction of NO (nitrogen oxide) within the coronary microcirculation might be the mechanism behind the increased vascular resistance[110]. Other studies have shown that oxygen breathing significantly decrease cardiac output and heart rate while increasing systemic vascular resistance[109,112].
Despite lack of robust evidence on the effects of supplementary oxygen, oxygen administration is widely recommended in international clinical practice guidelines[27,113-115], and current practice of oxygen administration is usually more liberal and results in hyperoxaemia[8,9,11-14]. Therefore, it is important that the potential benefit of supplemental

oxygen is weighed against the potential harmful effects of hyperoxaemia[116]. No former systematic review of randomised controlled trials with meta-analysis and Trial Sequential Analysis has been conducted so far.

In this review, we set out to assess the benefits and harms of higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation in intensive care patients.

We searched the following databases (on February 2016): Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue), MEDLINE (OvidSP), EMBASE (OvidSP), Science Citation Index (web of science), Biosis Previews (web of science), Cumulative Index to Nursing & Allied Health Literature (CINAHL), Allied and Complementary Medicine Datebase (AMED), Latin American Caribbean Health Sciences Literature (LILACS). We included randomised clinical trials, irrespective of publication status, reported outcomes, publication date, and language. We included any adult patient if they are admitted to or at the ICU when randomisation was performed. The interventions were a high target (liberal) and a low target (conservative) oxygenation strategy. Both mechanically ventilated patients and non-mechanically oxygenated patients were eligible for inclusion. We defined as the experimental group those receiving a high target (liberal) oxygenation strategy administered by any device to targets oxygen saturation, which aim is exposure to hyperoxaemia, either by high FiO_2 or high targets PaO_2 or SaO_2/SpO_2. We defined as the control group those receiving a low target (conservative) oxygenation strategy administered by any device, which aim is to minimize exposure to hyperoxaemia and reduce exposure to high FiO_2 or high targets PaO_2 or SaO_2/SpO_2. We required eligible studies to have a difference between the intervention and control groups of minimum 1 kPa in PaO_2, minimum 10% in FiO_2, or minimum 2% in SaO_2/SpO_2. We excluded trials assessing the effects of interventions with hyperbaric oxygen.

Results

We identified three trials includable for the analysis: Gomersall et al 2002[3], Girardis 2016[5] and Panwar 2016[4]. The Girardis et al trial was published after our search, but was included in our analysis. We rule out the possibility that other relevant studies were published in the meantime. However, we will update our search before writing the actual publication.

We also found a trial assessing the effect of hyperoxia and hypertonic saline on survival in patients with septic shock (ClinicalTrials.gov Identifier: NCT01722422)**.** Unfortunately it was terminated in 2014 and we could not retrieve any abstract.

Gomersall et al.[3] performed a randomised, controlled, single-blind trial study in a multidisciplinary intensive care unit of a university teaching hospital, investigating the effect of oxygen therapy on outcome and on symptomatic hypercapnia. Participants included patients admitted with a clinical diagnosis of an acute exacerbation of chronic obstructive pulmonary disease and a PaO_2 <6.6 kPa (50 mm Hg) and $PaCO_2$ >6.6 kPa (50 mm Hg) on air. Patients received oxygen therapy titrated to increase PaO_2 to >6.6 kPa (50 mm Hg) or >9 kPa (70 mm Hg). Patients in the low-oxygen tension group also received doxapram if they developed an acidosis with pH <7.2, whereas those in the high-oxygen tension group received doxapram if they developed symptomatic acidosis. Bronchodilator, steroid, and antibiotic therapy was standardized. Two patients in the low oxygen tension group (n _ 17) required mechanical ventilation and another one died. No patients in the high-oxygen group (n _17) had a poor outcome, two patients however, who required mechanical ventilation were excluded retrospectively. The trialists concluded that traditional teaching related to oxygen therapy for hypercapnic patients with an acute exacerbation of chronic obstructive pulmonary disease may be incorrect and that a large randomised, controlled study is required to confirm this impression. We evaluated the risk of bias as low, unclear of high for each of the following criteria: Random sequence generation (low), Allocation sequence concealment (low), Blinding of participants and personnel (high), Blinding of outcome assessment (unclear), Incomplete outcome data (high), Selective outcome reporting (unclear), Baseline imbalance (low), Early stopping (unclear). We evaluated the overall risk of bias for this study as 'high'.

Girardis et al.[5] performed a single-centre, open-label, randomised clinical trial to assess whether a conservative protocol for oxygen supplementation could improve outcomes in patients admitted to intensive care units (ICUs). Participants included all adults admitted with an expected length of stay of 72 hours or longer to the medical-surgical ICU of Modena University Hospital, Italy. The originally planned sample size was 660 patients, but the study was stopped early due to difficulties in enrolment after inclusion of 480 patients. Patients were randomly assigned to receive oxygen therapy to maintain PaO_2 between 70 and 100 mmHg or arterial oxyhemoglobin saturation (SpO_2) between 94% and 98% (conservative group) or, according to standard ICU practice, to allow PaO_2 values up to 150 mmHg or SpO_2 values between 97% and 100% (conventional control group). The primary outcome was ICU mortality. Secondary outcomes included occurrence of new organ failure and infection 48 hours or more after ICU admission. A total of 434 patients (median age, 64 years; 188 [43.3%] women) received conventional (n = 218) or conservative (n = 216) oxygen therapy and were

included in the modified intent-to-treat analysis. Daily time-weighted PaO_2 averages during the ICU stay were significantly higher ($P < 0.001$) in the conventional group (median PaO_2, 102 mmHg [IQR,88-116]) versus the conservative group (median PaO_2, 87mmHg [IQR, 79-97]). Mortality was lower in the conservative oxygen therapy group. They concluded that among critically ill patients with an ICU length of stay of 72 hours or longer, a conservative protocol for oxygen therapy versus conventional therapy resulted in lower ICU mortality although those preliminary findings were based on unplanned early termination of the trial. The trialists concluded that a larger multicentre trial is needed to evaluate the potential benefit of this approach. We evaluated the risk of bias as low, unclear or high for each of the following criteria: Random sequence generation (low), Allocation sequence concealment (low), Blinding of participants and personnel (high), Blinding of outcome assessment (unclear), Incomplete outcome data (low), Selective outcome reporting (low), Baseline imbalance (low), Early stopping (high). We evaluated the overall risk of bias for this study as 'high'.

Panwar et al.[4] performed a pilot multicentre randomised controlled trial to determine whether a conservative oxygenation strategy is a feasible alternative to a liberal oxygenation strategy among ICU patients requiring invasive mechanical ventilation (IMV). 103 adult patients deemed likely to require invasive mechanical ventilation for more than 24 hours were randomly allocated to either a conservative oxygenation strategy with target oxygen saturation as measured by pulse oximetry (SpO_2) of 88–92% (n = 52) or a liberal oxygenation strategy with target SpO_2 of greater than or equal to 96% (n = 51).The mean area under the curve and 95% confidence interval (CI) for SpO_2 (93.4% [92.9–93.9%] versus 97% [96.5–97.5%]), SaO2 (93.5% [93.1–94%] versus 96.8% [96.3–97.3%]), PaO_2 (70 [68–73] mm Hg versus 92 [89–96] mm Hg), and FIO_2 (0.26 [0.25–0.28] versus 0.36 [0.34–0.39) in the conservative versus liberal oxygenation arm were significantly different (P< 0.001 for all). There were no significant between-group differences in any measures of new organ dysfunction, or ICU or 90-day mortality. The percentage time spent with SpO_2 less than 88% in conservative versus liberal arm was 1% versus 0.3% (P = 0.03), and percentage time spent with SpO_2 greater than 98% in conservative versus liberal arm was 4% versus 22% (P = 0.001). The adjusted hazard ratio for 90-day mortality in the conservative arm was 0.77 (95% CI, 0.40–1.50; P = 0.44) overall and 0.49 (95% CI, 0.20–1.17; P = 0.10) in the prespecified subgroup of patients with a baseline PaO_2/FiO_2 less than 300 mmHg. The trilaists concluded that the feasibility of a conservative oxygenation strategy in patients receiving IMV and that larger randomised controlled trials of this intervention appear justified. We evaluated the risk of bias as low,

unclear of high for each of the following criteria: Random sequence generation (low), Allocation sequence concealment (low), Blinding of participants and personnel (high), Blinding of outcome assessment (unclear), Incomplete outcome data (low), Selective outcome reporting (low), Baseline imbalance (low), Early stopping (low). We evaluated the overall risk of bias for this study as 'high'.

Two authors (Sara Russo Krauss and Olav Lilleholt Schjørring) independently extracted data from the three trials.

We analysed the results of the three above mentioned articles by performing meta-analysis of all cause mortality at maximum follow up by using the statistical software Review Manager (RevMan 2014) provided by the Cochrane Collaboration. For the Girardis et al trial, we reported the mortality data on the modified intent to treat population. We calculated risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes. We assessed our intervention effects with either random-effects model or fixed-effects model. Based on the above parameters we concluded that the meta-analysis of these three trials did not provide a significant difference between the intervention and the control group on all cause mortality on maximum follow up (**Figure 1.a,b,c,d,).**

Figure 1a: Random Effect

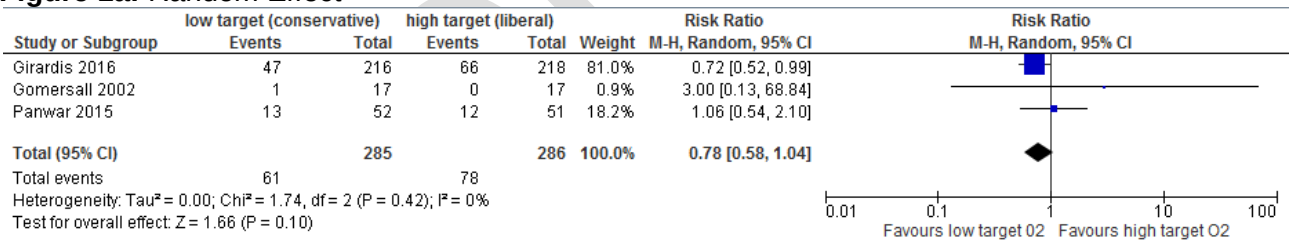


Figure 1b: Random Effect (swapped)

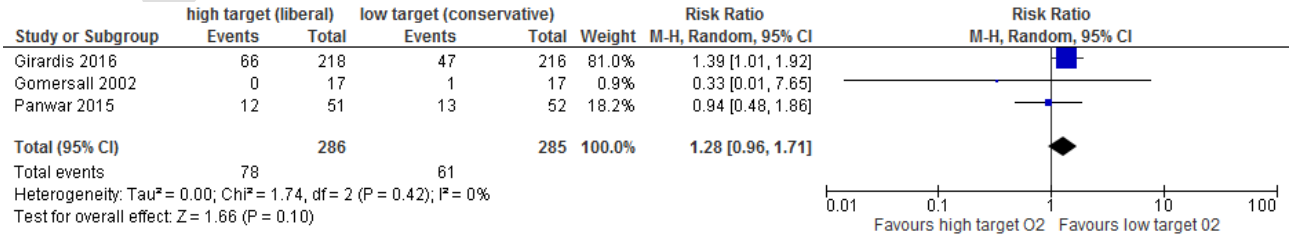


Figure 1c: Fixed Effect

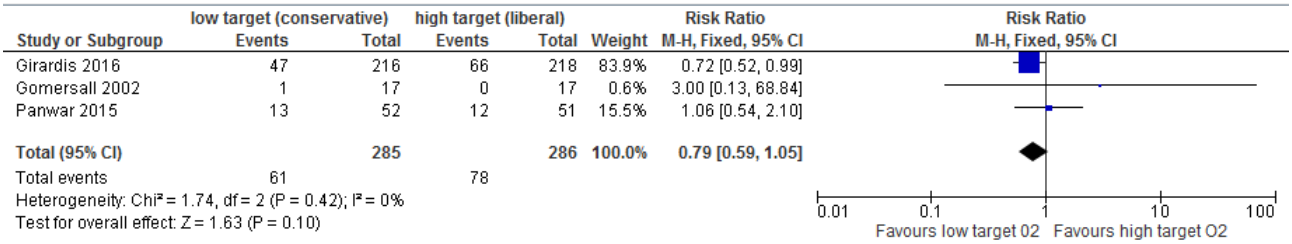
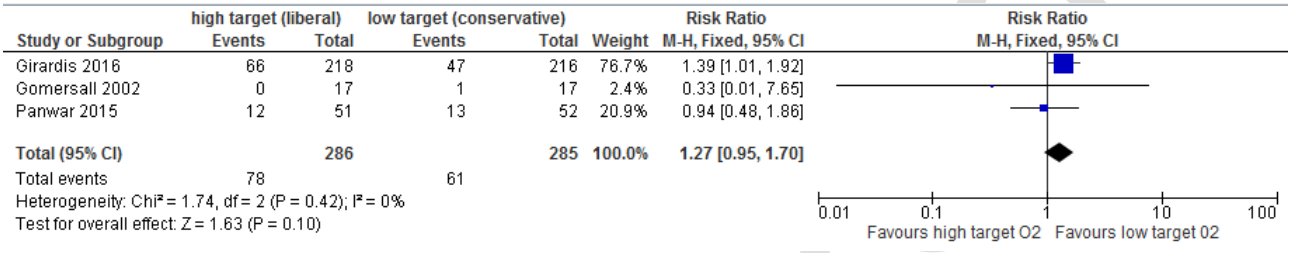


Figure 1d: Fixed Effect (swapped)



Since the use of doxapram as a co-intervention in the trial by Gomersall et al. is not distributed equally, we generated a series of figures excluding this trial (**Figure 1 a,b,c,d**). Doxapram was administered with slightly different indications in the two intervention groups and one could therefore argument that the trial should not be included in our analysis.

Figure 2a: Random Effect without Gomersall 2002

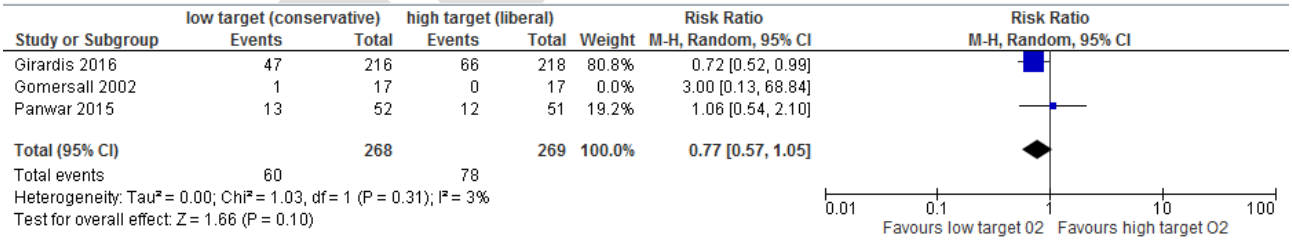


Figure 2b: Random Effect without Gomersall 2002 (swapped)

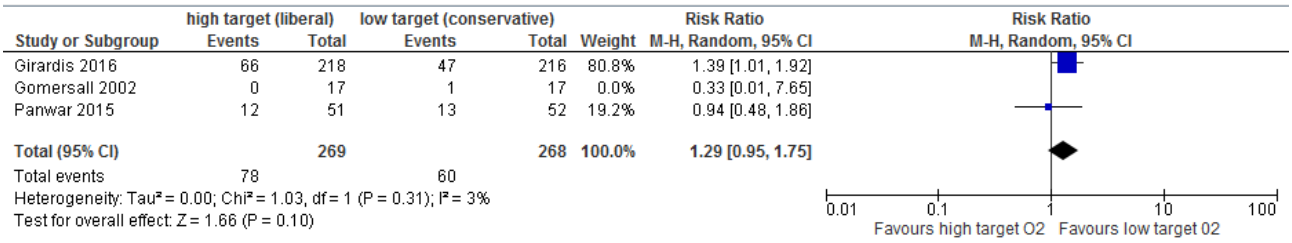


Figure 2c: Fixed Effect without Gomersall 2002

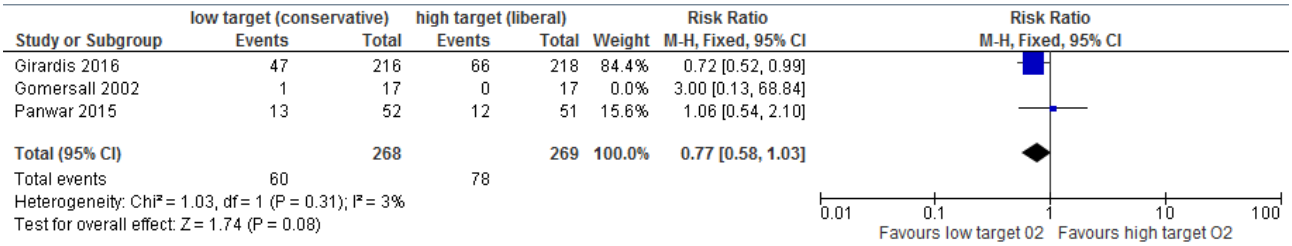
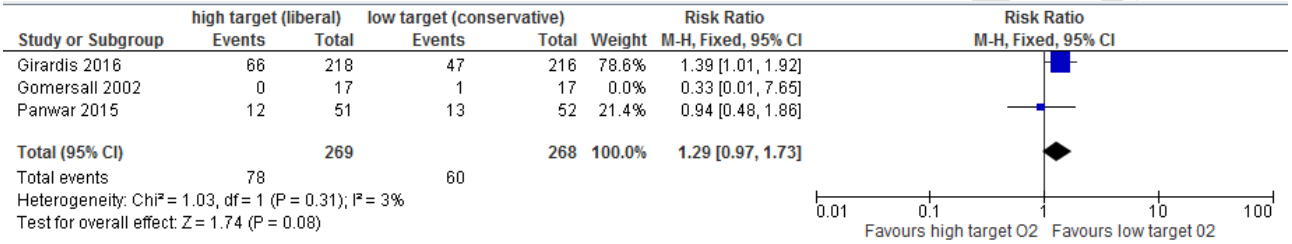


Figure 2d: Fixed Effect without Gomersall 2002 (swapped)



We analysed mortality outcome with TSA **Figure 3**. Trial Sequential Analysis (TSA) shows that the actual meta-analysis of the accrued 571 participants is not more than 12% of the required information size of 2652 participants to detect or reject an effect of 20% relative risk reduction (RRR) with a control proportion of mortality of 27% in the high oxygen target group. Diversity is set to the actual 0% in the present meta-analysis and alfa=0.05 and beta=0.10. The TSA adjusted confidence interval (CI) for the relative risk (RR) of 0.78 is 0.39 to 1.57 while the naive unadjusted CI is 0.58 to 1.04. As none of the trial sequential monitoring boundaries are crossed there is no evidence to conclude on the RRR suggested by these three trials and the uncertainty on an intervention effect of 20% RRR is huge.

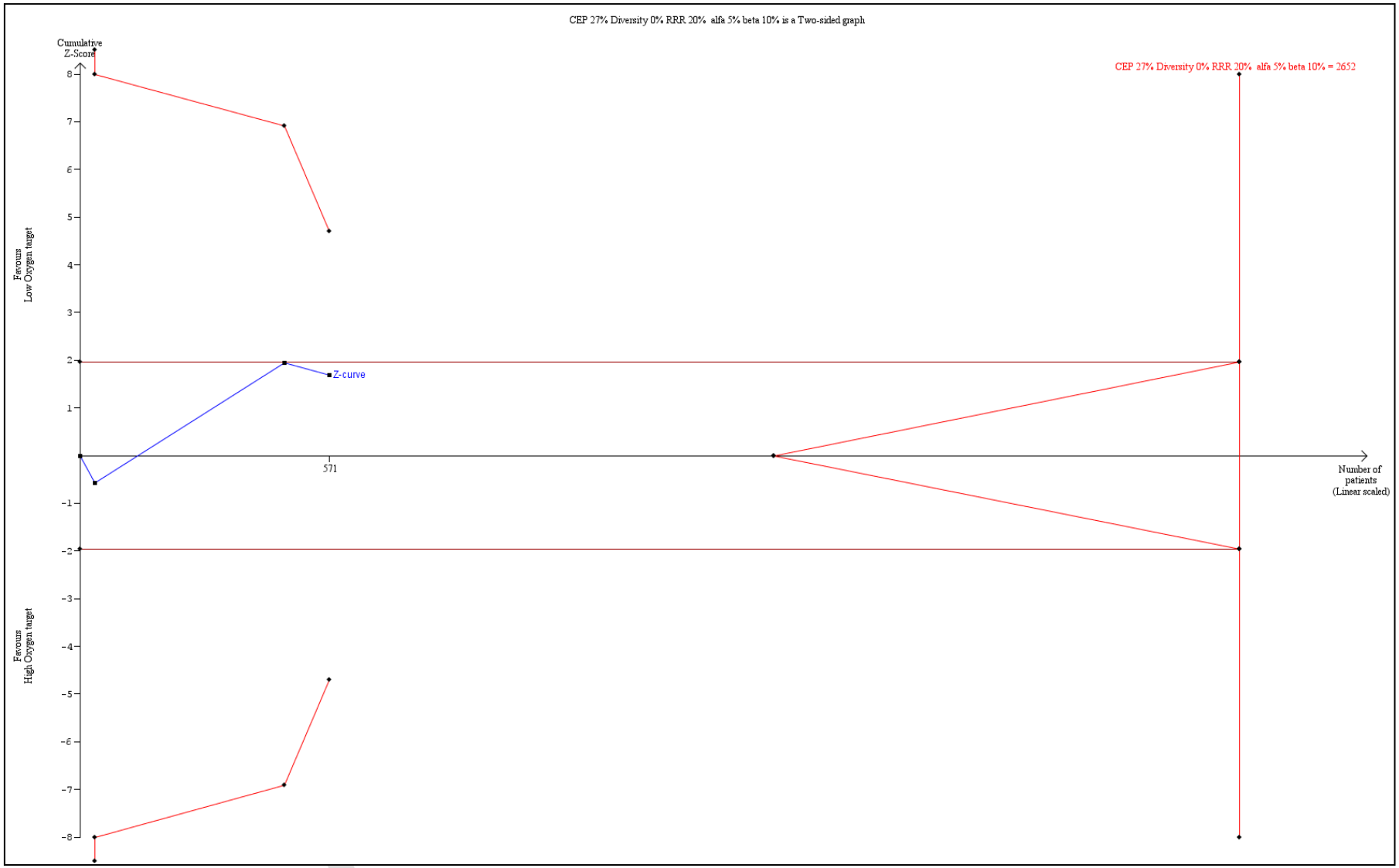

CEP 27% Diversity 0% RRR 20% alfa 5% beta 10% is a Two-sided graph
Cumulative Z-Score
CEP 27% Diversity 0% RRR 20% alfa 5% beta 10% = 2652
Favours Low Oxygen target
Favours High Oxygen target
Z-curve
571
Number of patients (Linear scaled)
8
7
6
5
4
3
2
1
-1
-2
-3
-4
-5
-6
-7
-8

Fig.3

We reported the risk of bias for the three trials in the table below (Table 1.)

Table 1.

Trial	Random sequence generation	Allocation sequence concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Baseline imbalance	Early stopping	Overall risk of bias
Gomersall 2002	low	low	high	unclear	high	unclear	low	unclear	high
Panwar 2015	low	low	high	unclear	low	low	low	low	high
Girardis 2016	low	low	high	unclear	low	low	low	high	high

Conclusion

In the meta-analysis of the results on all-cause mortality in three published trials with overall high risk of bias there is not sufficient evidence to conclude that neither a high nor a low oxygenation target is the superior intervention in ICU patients. The unweighted mortality in the high oxygenation target groups is 27% and the between trial heterogeneity of the intervention effect was zero (I^2=0 and D^2=0). The required information to detect or reject a 20% RRR was 2,652 and only 22% of this required information has presently been accrued, none of the trial sequential monitoring boundaries has been crossed and the evidence is presently inconclusive, however the point estimate of a 22% RRR is presently in favour of using a low oxygenation target for ICU patients. The assumption that heterogeneity will be zero when further trials are reported will probably have to change and the required information size and the corresponding number of trials may most likely increase. The 2 x 2 factorial trial Hyper2S also investigating a low versus a high oxygen target (as one of the interventions involved) has been stopped due to a 9% excess mortality in the high oxygen target group. Three more trials are presently being conducted and should be followed closely during the process of randomising patients in the HOT-ICU trial.

Appendix 11. International Committee of Medical Journal Editors (ICMJE) form for potential conflicts of interest

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

1

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) | 2. Surname (Last Name) | 3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication.**

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

2

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☐ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

3