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Higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation for adult intensive care patients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation in adults in intensive care units.

BACKGROUND

Description of the condition

Hypoxaemia refers to low oxygen tension in arterial blood and is usually defined in terms of partial pressure of arterial oxygen (PaO₂) or arterial oxygen saturation of haemoglobin (SaO₂) (O'Driscoll 2008). Additionally, the non-invasive peripheral oxygen saturation (SpO₂) measured by pulse oximetry is routinely used. Hypoxaemia refers directly to the levels of oxygen in the blood, while the term hypoxia is defined as the lack of oxygen in

specified compartments; for example, tissues, organs, alveoli or the body as a whole (O'Driscoll 2008).

In healthy individuals, the normal range for PaO₂ at sea level is 80 mmHg to 100 mmHg (Kratz 1998), depending on body position and with a general decrease with age (O'Driscoll 2008). There is no clear definition of hypoxaemia. The most widely used definitions are a PaO₂ below 60 mmHg or an SaO₂ below 90% (O'Driscoll 2008). However, oxygenation targets below the normal range and even defined as hypoxaemic is recommended in adults who are mechanically ventilated with acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) targeting PaO₂ of 55 mmHg to 80 mmHg or SpO₂ of 88% to 95% (ARDS Network

2000; Brower 2004).

In ICU patients hypoxaemia is a common clinical manifestation of inadequate gas exchange in the lungs (Petersson 2014). The condition can arise primarily from four different mechanisms: hypoventilation, ventilation/perfusion (V/Q) mismatch, intrapulmonary right-to-left blood shunting, or diffusion impairment, or a combination of these (Petersson 2014; Roussos 2003). Hypoventilation in the ICU is typically caused by an acute depression of the central nervous system (CNS) either through administration of sedative or analgesic agents or due to critical illness with indirect (e.g. circulatory, hypoxic or hypercapnic failure) or with direct (e.g. traumatic brain injury, intracranial haemorrhage or meningoencephalitis) cerebral affection. Hypoxaemia due to hypoventilation is always accompanied by hypercapnia since hypoventilation affects the alveolar clearance of carbon dioxide to a larger degree than the alveolar oxygenation and hypoventilation does not affect the alveolar-arterial gradient (Petersson 2014; Roussos 2003). V/Q mismatch with a low V/Q ratio evolves when ventilation in certain lung regions is disproportionally decreased as compared to perfusion. This is seen in various conditions (Petersson 2014), including pneumonia, ARDS, pulmonary oedema and chronic obstructive pulmonary disease (COPD) (Kent 2011). The impact of a low V/Q ratio is partially compensated by physiological hypoxic pulmonary vasoconstriction in the affected segments of the lung (Rodríguez-Roisin 2005). V/Q mismatch with a high V/Q ratio evolves when perfusion in certain lung regions is disproportionally decreased as compared to ventilation, as is classically seen in pulmonary embolism (Petersson 2014), but are also prevalent in COPD (Wagner 1977) and ARDS (Donahoe 2011). Intrapulmonary shunting is the consequence of complete V/Q mismatch with abolished ventilation which allows the passing of blood through sections of the pulmonary vascular bed without being oxygenated. This is seen in all types of pulmonary atelectasis (including absorption atelectasis) and is especially prevalent in ARDS and pneumonia (Petersson 2014). V/Q mismatch and intrapulmonary shunting are the most common causes of hypoxaemia in the ICU (Petersson 2014). Diffusion impairment occurs when the diffusion pathway for oxygen from the alveolar space to the pulmonary capillaries is pathologically increased, either acute as seen in pneumonia, pulmonary oedema or ARDS or chronically as seen in the large group of interstitial lung diseases (Petersson 2014).

Description of the intervention

Administration of supplemental oxygen, defined as fraction of inspired oxygen (FiO₂) above 21%, is a frequent intervention in ICU patients. Oxygen is often administered during acute conditions in the prehospital setting and during hospital admission. Patients admitted to the ICU often receive mechanical ventilation and oxygen support to correct or prevent hypoxaemia. Treatment is usually a combination of ventilatory (Esan 2010), and non-

ventilatory (Raouf 2010), strategies where the aim is to reduce morbidity and mortality associated with hypoxaemia by restoring arterial oxygenation to normal values. Due to the administration of oxygen, patients often achieve supranormal levels of PaO₂ (de Graaff 2011; de Jonge 2008; Eastwood 2012; Itagaki 2015; Suzuki 2013).

Oxygen strategies used to treat hypoxaemia ICU patients, are in some studies associated with harm, possibly because the patients who receive oxygen are the most ill but it might also be that 'too much' oxygen is as harmful as 'too little' (Kallet 2013). The harms associated with lung injury caused by ventilator as well as oxygen toxicity followed by high FiO₂ may exceed the benefit of normalizing oxygenation (PaO₂ and SaO₂).

How the intervention might work

The purpose of oxygen therapy is to increase oxygen delivery to tissues. Tissue hypoxia can cause cell death, but the precise level at which this occurs has not been determined, and the level might differ between individuals (O'Driscoll 2008).

Supplemental oxygen therapy has potentially several advantages, including maintenance of delivery of oxygen to tissues, prevention of organ dysfunction followed by anoxic injury and an increase in the right-sided heart function as a reaction of pulmonary arterial vasodilation (Budinger 2013).

Several additional beneficial effects of supplemental oxygen have been proposed and include: 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; antiapoptotic effects in brain and myocardium; normalization of cerebral extracellular homeostasis and stabilization of the blood-brain barrier (Tan 2014).

High inspiratory oxygen concentrations have been associated with adverse outcomes in emergency medical conditions, including exacerbation of COPD (Austin 2010), resuscitation after cardiac arrest (Kilgannon 2010), myocardial infarction (Cabello 2016), and traumatic brain injury (Brenner 2012). Additionally, treating perioperative patients with a high FiO₂ may be associated with increased mortality without reducing surgical site infections in surgical patients (Wetterslev 2015). These adverse outcomes may be caused by decreased local blood flow on normal and non-diseased vasculature induced by the vasoconstriction effect of hyperoxaemia (Sjöberg 2013), which have been described in the vascular system, for example, in heart (Kenmure 1971), and brain (Watson 2000). Knowledge on cell biology also suggests that oxygen might have harmful effects. Prolonged exposure to hyperoxia causes lung injury, which is thought to be caused by the production and accumulation of reactive oxygen species that overwhelm natural antioxidant defences and destroy cellular structures (Kallet 2013). Exposure to a lethal dose of hyperoxia is associated with a boost in the production of reactive oxygen species, which eventually

overwhelms the cell repair processes and thereby causes cell injury (Crapo 1986). It has been proposed that reactive oxygen species may trigger apoptosis within pulmonary cells leading to necrosis and thereby causing an inflammation which damages lung tissue further (Zaher 2007).

The mechanical ventilation in itself might also be associated with complications and include increased risk of pneumonia, impaired cardiac performance and neuromuscular problems relating to sedation and muscle relaxants (Whitehead 2002). In addition, applying pressure to the lungs can cause damage known as ventilator-induced lung injury. Ventilator associated lung injury has been shown to be augmented by hyperoxia in animal studies (Bailey 2003; Sinclair 2004).

Why it is important to do this review

The mainstay treatment for hypoxaemia is oxygen therapy, which is given to the vast majority of ICU patients. For example, mechanical ventilation is each year given to two to three million ICU patients (Adhikari 2010; Wunsch 2010), and is associated with morbidity (Kahn 2010), and mortality (Metnitz 2009; Wunsch 2010). The annual cost is estimated at USD 15 billion to USD 27 billion solely in high-income countries (Dasta 2005; Wunsch 2010).

Current practice of oxygen administration is usually more liberal and results in hyperoxaemia (de Graaff 2011; de Jonge 2008; Itagaki 2015; Panwar 2013; Rachmale 2012; Suzuki 2013). Some studies have indicated an association between hyperoxaemia and mortality (Dahl 2015; Kilgannon 2010; Meyhoff 2012), other studies have not (Bellomo 2011; Eastwood 2012; Raj 2013; Young 2012). Two meta-analyses of observational data found an association between hyperoxaemia and mortality after cardiac arrest, stroke and traumatic brain injury (Damiani 2014), and overall across critically ill patients (Helmerhorst 2015). Permissive hypoxaemia has been studied by Gilbert-Kawai et al (Gilbert-Kawai 2014), who compared permissive hypoxaemia to normoxaemia in critically ill patients in a systematic review but found no relevant randomized controlled trials (RCTs).

Although the possible adverse effects of hyperoxaemia are known, prevention of hypoxia through hyperoxaemia seems to be prioritized (Pannu 2016).

There is uncertainty about defining the ideal target oxygenation for ICU patients due to limited evidence from RCTs. Despite lack of robust evidence of effectiveness, oxygen administration is widely recommended in international clinical practice guidelines (AARC 2002; ARC 2014; Dellinger 2013; O'Driscoll 2008). Panwar et al (Panwar 2015), and Girardis et al (Girardis 2016), published data on RCTs comparing higher to lower oxygenation targets in ICU patients, and Asfar et al (Asfar 2017) published data on an RCT comparing extreme hyperoxaemia versus conventional oxygenation throughout the first 24 hours of ICU admission in adults with septic shock. Additional RCTs comparing high versus low

targeted oxygen therapy in the critically ill are ongoing and may soon be published (ACTRN12615000957594; NCT02321072; NCT02378545).

Oxygen is a common intervention in ICU patients and might have beneficial effects as well as harmful effects (Hafner 2015). The potential benefit of supplemental oxygen must be weighed against the potential harmful effects of hyperoxaemia (Jakobsen 2013). No former systematic review of RCTs with meta-analysis and Trial Sequential Analysis (TSA) has been conducted.

OBJECTIVES

To assess the benefits and harms of higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation in adults in intensive care units.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs, irrespective of publication status, reported outcomes, publication date, and language.

We will include unpublished trials only if methodological descriptions and trial data are provided by direct contact with trial authors or in written form.

We will exclude randomized cross-over trials and quasi-randomized trials.

Types of participants

We will include any adult aged 18 years or older admitted to the ICU. Participants will be included only if they are admitted to the ICU when randomization is allocated.

Types of interventions

We will include trials having a clear differentiation of participants randomized to either a high target (liberal) or a low target (conservative) oxygenation strategy. Both mechanically ventilated and non-mechanically oxygenated patients will be eligible for inclusion. To be able to include all relevant trials, we will not use pre-defined arbitrary thresholds of oxygenation for the two groups.

Intervention group: adults receiving a high target (liberal) oxygenation strategy administered by any device to target oxygen saturation, the aim of which is exposure to hyperoxaemia, either by high FiO₂ or high target PaO₂ or SaO₂/SpO₂.

Control group: adults receiving a low target (conservative) oxygenation strategy administered by any device, the aim of which is to minimize exposure to hyperoxaemia and reduce exposure to high FiO_2 or high target PaO_2 or $\text{SaO}_2/\text{SpO}_2$.

We require 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 $\text{SaO}_2/\text{SpO}_2$.

We will exclude trials/groups randomized to permissive hypoxaemia (FiO_2 below 0.21, $\text{SaO}_2/\text{SpO}_2$ below 80% and PaO_2 below 6 kPa). Furthermore, we will exclude interventions with hyperbaric oxygen.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Proportion of participants with one or more serious adverse event (SAE), defined as a dichotomous outcome according to patients having at least one SAE or none. Therefore, we will use the risk ratio (RR) of the proportion of participants with one or more SAE in the two groups (intervention versus control). We will note an SAE if the trialists report it/them as SAE according to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) (ICH-GCP 1997). In addition, we will note the following as SAEs: new-onset respiratory, cardiovascular, liver or renal failure (defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or greater for the corresponding organ) occurring 48 hours or more after ICU admission; need for reoperation in surgical patients; and bloodstream, respiratory and surgical site infections. We will consider all other adverse events as non-serious.
3. Quality of life (any valid scale such as 36-item Short Form (SF-36)).

Secondary outcomes

1. Lung injury diagnosed after randomization (composite outcome). This composite outcome will be defined as either: ARDS (defined by the onset of a known clinical insult within one week or acute worsening of respiratory symptoms; chest imaging; origin of oedema; and oxygenation may be mild, moderate or severe (ARDS Definition Task Force 2012), or as defined by trialists); pulmonary fibrosis (defined as evolved from any cause) or as defined by trialists) or pneumonia (defined as pneumonia occurring 48 hours or more after admission in non-intubated patients or pneumonia arising more than 48 to 72 hours after endotracheal intubation (ATS 2005), or as defined by trialists. As a secondary analysis, we will analyse each component of the composite outcome separately.
2. Acute myocardial infarction diagnosed after randomization (defined as the demonstration of myocardial cell death due to

significant and sustained ischaemia (Thygesen 2012), or as defined by trialists).

3. Stroke diagnosed after randomization (defined as central nervous system (CNS) infarction, ischaemic stroke, silent CNS infarction, intracerebral haemorrhage, stroke caused by intracerebral haemorrhage, silent cerebral haemorrhage, subarachnoid haemorrhage, stroke caused by subarachnoid haemorrhage, stroke caused by cerebral venous thrombosis and stroke not otherwise specified (Sacco 2013), or as defined by trialists).

4. Severe sepsis diagnosed after randomization (defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Dellinger 2013), or as defined by trialists). We will estimate all continuous and dichotomous outcomes at two time points:

1. Time point closest to three months. This will be our assessment time point of primary interest;
2. Maximum follow-up, as reported by trialists.

Search methods for identification of studies

Electronic searches

We will identify RCTs that fulfil the inclusions criteria through literature searching with systematic and sensitive search strategies specifically designed to identify relevant RCTs without restrictions to language, publication year and journal.

We will search the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue) (Appendix 1);
2. MEDLINE (OvidSP) (Appendix 2);
3. Embase (OvidSP) (Appendix 3);
4. Science Citation Index (Web of Science) (Appendix 4);
5. Biosis Previews (Web of Science) (Appendix 5);
6. Cumulative Index to Nursing & Allied Health Literature (CINAHL) (Appendix 6);
7. Allied and Complementary Medicine Database (AMED) (Appendix 7);
8. Latin American Caribbean Health Sciences Literature (LILACS) (Appendix 8).

Searching other resources

We will manually screen the reference lists of reviews, relevant papers, randomized and non-randomized trials, and editorials for potentially relevant trials. Furthermore, we will contact authors on identified studies, experts for each area and pharmaceutical companies (if relevant) and ask for knowledge of additional (also unpublished) trials.

In addition, we will search for ongoing and unpublished trials using the following trial registers:

1. ClinicalTrials.gov (ClinicalTrials.gov);
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/en/);
3. EU clinical trial register (www.clinicaltrialsregister.eu/);
4. Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/).

Data collection and analysis

We will use the following methods for data collection and data analyses.

Selection of studies

Two review authors (MB and OS) will independently screen the titles and abstracts of all reports identified by the searches. We will obtain the full text of reports which are deemed potentially relevant, and the same two review authors will independently assess these for inclusion, and resolve any disagreement by consensus.

Data extraction and management

Two review authors (MB and OS) will independently extract pre-defined data of the included trials using a data collection form ([Appendix 9](#)), which was specifically designed and piloted by the review team. We will resolve any disagreement concerning the extracted data by discussion. If no agreement can be reached, a third review author (JW) will resolve the issue. When necessary, we will contact corresponding authors to clarify issues relating to data reporting or if further study details are needed.

Assessment of risk of bias in included studies

Two review authors (MB and OS) will independently assess the methodological quality of each included trial, defined by the design of the trial and reporting. We will resolve any disagreement by discussion. We will assess the risk of bias according to the *Cochrane Handbook of Systematic reviews of interventions* ([Higgins 2011a](#)), using the details in [Appendix 10](#).

For all included trials, we will assess the following risk of bias domains: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other bias risk and overall risk of bias. In addition, we will assess the domains 'Blinding of outcome assessment', 'Incomplete outcome data' and 'Selective outcome reporting' for each outcome. Thus, we will be able to assess the bias risk for each result. Based on this assessment, the included trials and each outcome result will be defined as low risk of bias if all bias domains are judged at low risk of bias.

We will prepare a summary assessment of the risk of bias across trials and for each important outcome (across domains) by preparing a 'Summary of findings' table, 'Risk of bias' graph and a 'Risk of bias' summary figure ([Higgins 2011a](#)).

Measures of treatment effect

We will calculate RR with 95% confidence interval (CI) and TSA adjusted CI for dichotomous outcomes. For continuous outcomes, we will include both end scores and change scores in the analyses. End scores will be used if both are reported. We will calculate mean difference (MD) and standardized mean difference (SMD) with 95% CIs and TSA adjusted CIs for continuous outcomes.

Unit of analysis issues

If the search finds multi-arm trials that compare, for example, three different oxygenation targets, we will combine the two experimental intervention groups of the study (if they each fulfil the minimum difference compared with the control group of 1 kPa in PaO₂, 10% in FiO₂ and 2% in SaO₂/SpO₂) into a single group and compare these to the control group. If only one of the experimental groups fulfils the minimum difference to the control, we will compare this group to the control group.

If the search finds a multi-arm trial that compares, for example, three different oxygenation targets, where the control group is the middle group, and the minimum difference in oxygenation target is fulfilled, we will compare the higher oxygenation group to the control group, as the lower group will be excluded due to being randomized to an extreme permissive hypoxaemia.

If the search finds cluster-randomized trials, we will define the ICU as the unit of allocation. We will use the generic inverse variance method in Review Manager 5 to calculate effect estimates for these trials ([RevMan 2014](#)).

Dealing with missing data

We will contact trial investigators of the original report for important missing data.

For both dichotomous and continuous outcomes, we will not impute missing data for any outcomes in the primary analysis and will not use intention-to-treat data if the original report did not contain such data.

If trials do not report standard deviations (SD), we will calculate the SDs using data from the trial if possible.

In the sensitivity analysis for dichotomous and continuous outcomes, we will use imputed data (see [Sensitivity analysis](#)).

Assessment of heterogeneity

We will assess signs of heterogeneity by visual inspection of the forest plots.

We will assess presence of statistical heterogeneity using the Chi² test with significance set at P less than 0.10 and by measuring the quantities of heterogeneity using the I² statistic (Higgins 2003). Overall, we will consider an I² statistic of 0% to 40% as not important, 30% to 60% as moderate, 50% to 90% as substantial and 75% to 100% as considerable heterogeneity (Higgins 2011a). High statistical heterogeneity is generally more present when meta-analysing continuous outcomes (Alba 2016). Because we anticipate large clinical heterogeneity as well as statistical heterogeneity, we will generally prefer reporting the result from a random-effects model. However, if one or two trials dominates the acquired evidence (e.g. with more than 80% of the randomized participants (Higgins 2002; MAGIC 2002; Woods 2002)), the random-effects model may grossly overestimate the intervention effect and in this situation, we will report primarily the result from the fixed-effect model. Hence, we will primarily report the result from the model with the most conservative point estimate of the two (Jakobsen 2014), being the estimate closest to zero effect. If the two estimates are approximately equal, we will use the estimate with the widest CI.

We will explore potential clinical heterogeneity by conducting the prespecified subgroup analyses (see [Subgroup analysis and investigation of heterogeneity](#)), which may explain the statistical heterogeneity.

Assessment of reporting biases

We will visually assess funnel plots for signs of asymmetry if an analysis includes 10 or more trials (Higgins 2011a; Jakobsen 2014).

We will test asymmetry within dichotomous outcomes using the Harbord test (Harbord 2006), and for continuous outcomes regression using the asymmetry test (Egger 1997). Adjusted rank correlation will be used (Begg 1994).

Data synthesis

Meta-analysis

We will undertake the systematic review according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and Keus and colleagues (Keus 2010), as well as the eight-step assessment suggested by Jakobsen et al (Jakobsen 2014). We will perform meta-analysis of outcomes with comparable effect measures where more than one trial is included. If clinical and statistical heterogeneity are large or unexpected, we will reconsider doing the meta-analysis. We will use the statistical software Review Manager 5 (RevMan 2014) provided by Cochrane and the TSA (TSA 2011) software version 0.9 CTU to meta-analyse data.

Assessment of significance

We will assess our intervention effects with both random-effects model meta-analyses (Deeks 2010; DerSimonian 1986; Mantel 1959), and fixed-effect model meta-analyses (DeMets 1987; Mantel 1959).

We use three primary outcomes and, therefore, we will consider a P value of 0.025 or less as statistically significant analysing the primary outcomes (Jakobsen 2014; Jakobsen 2016). We will use four secondary outcomes and, therefore, we will consider a P value of 0.02 or less as statistically significant analysing the secondary outcomes (Jakobsen 2014). We will use the eight-step procedure to assess if the thresholds for significance are crossed (Jakobsen 2014).

Trial Sequential Analysis

The chance of type I error (a false-positive finding) is increased when multiple testing is done (e.g. when analysing multiple primary and secondary outcomes or repeated testing of the data). In small studies, notably for binary outcomes, type I error is likely because the effect estimates tend to be more unstable (Mascha 2015). In meta-analyses the chance of finding a type I error is increased when they are updated over time when new trials are added (Mascha 2015). Cochrane recommends all systematic reviews to be updated every second year making the multiplicity issue highly important to adjust for. Current practice often uses a 0.05 significance criterion each time meta-analyses are updated, thus increasing the overall chance of a type I error (Mascha 2015). In addition, type II error (the probability of missing true findings) is a problem in many meta-analyses, due to sparse data. Statistically significant meta-analyses with few participants have low reliability, and the interventional effect is often overrated (Turner 2013). In a random sample of 50 meta-analyses of anaesthesiological interventions with dichotomous outcome variables, Imberger et al found 88% of the meta-analyses to be underpowered, meaning that although significant at P less than 0.05, the meta-analyses should have included more participants (Imberger 2015). Furthermore, only 32% of the meta-analyses preserved the risk of type I error at 5% or less when powered for detecting a relative risk of 20% between groups (Imberger 2015).

Consequently, cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Brok 2009; Higgins 2011b; Imberger 2015; Mascha 2015; Pogue 1997; Terkawi 2016; Thorlund 2009; Wetterslev 2008), and TSA (Imberger 2016; TSA 2011), can be applied to assess this risk (Gluud 2011). The required information size and the required number of trials (Kulinskaya 2014) (i.e. the number of participants and trials needed in a meta-analysis to detect or reject an a priori prespecified realistic intervention effect) can be calculated in order to minimize random errors (Wetterslev 2009). The required information size takes into account the event proportion in the control group, the assumption of a plausible rel-

ative risk reduction (RRR) and the heterogeneity variance (Turner 2013), of the meta-analysis (Wetterslev 2009). TSA enables testing for significance to be conducted each time a new trial is included into the meta-analysis. On the basis of the required information size and the required number of trials, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size (Imberger 2015; Mascha 2015; Terkawi 2016; Wetterslev 2008).

Firm evidence for benefit or harms may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case further trials may turn out to be superfluous. In contrast, if the boundary is not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z-score crosses the trial sequential monitoring boundaries for futility. We will use relatively conservative estimations of the anticipated intervention effect estimates to reduce the risk of random error (Jakobsen 2014). Large anticipated intervention effects lead to small required information sizes and the thresholds for significance will be less strict after the information size has been reached (Jakobsen 2014).

We will analyse all primary and secondary outcomes with TSA. We will estimate the diversity-adjusted required information size (Wetterslev 2009), based on the proportion of participants with an outcome in the control group. In addition, we will use a family wise error rate (FWER) of 5% (Jakobsen 2014), leading to a statistical significance level of 2.5% for each of the co-primary outcomes, a beta of 20% and a diversity (D^2) (Wetterslev 2009) suggested by the trials in the meta-analysis (Jakobsen 2014). We will present TSA-adjusted CIs (Gluud 2011). As a sensitivity analysis, we will use a diversity of 20% if the actual measured heterogeneity is in fact zero because in this case heterogeneity will most likely increase when further trials are added until the required information size is reached. As anticipated intervention effects for the primary and secondary outcomes in the TSA, we will use realistic a priori RRR or increase of 20% RRR or a 20% relative risk increase (RRI). Furthermore, we will use an RRR or a RRI based on the confidence limit closest to null effect in the 95% CI in the traditional meta-analysis.

Subgroup analysis and investigation of heterogeneity

We will meta-analyse all included trials regardless of oxygenation strategy (PaO_2 , SaO_2 , SpO_2 , FiO_2). We believe a meta-analysis of the specified strategies is feasible, as the amount of oxygen absorbed overlap to a great extent. Whether FiO_2 is raised or the aim is a higher target PaO_2 the result is that more oxygen is delivered and the PaO_2 will be elevated in both strategies. However, we recognize that especially in adults with ARDS there are adults where it would

be extremely difficult to reach a predefined target of PaO_2 by either strategy but certainly both strategies would expose the lungs to high oxygen levels, while other adults may subsequently develop different PaO_2 levels by the two strategies.

We will seek to determine if the efficacy and safety of the treatment options are influenced by types of ICU populations and type of oxygen administration.

We will perform the following subgroup analyses if data permit:

1. Trials with overall high risk of bias compared to trials with overall low or uncertain risk of bias.
2. According to different types of oxygen interventions:
 - i) oxygen level defined by FiO_2 (as defined and set by trialists);
 - ii) oxygenation target measured using PaO_2 (as defined by trialists);
 - iii) oxygenation target measured using SaO_2 or SpO_2 (as defined by trialists);
 - iv) oxygenation target measured using either PaO_2 or SaO_2 or SpO_2 (as defined by trialists).
3. According to FiO_2 or oxygenation/target in the higher-oxygen-administration group:
 - i) low targets defined as FiO_2 of 0.5 or lower or PaO_2 of 10 kPa or lower or $\text{SaO}_2/\text{SpO}_2$ of 95% or lower;
 - ii) high targets defined as FiO_2 above 0.5 or PaO_2 above 10 kPa or $\text{SaO}_2/\text{SpO}_2$ above 95%.
4. According to FiO_2 or oxygenation/target in the lower-oxygen-administration group:
 - i) low targets defined as FiO_2 between or at 0.21 to 0.30 or PaO_2 between or at 6 kPa to 8 kPa or $\text{SaO}_2/\text{SpO}_2$ between or at 85 to 90%;
 - ii) high targets defined as FiO_2 above 0.30 to 0.40 or PaO_2 above 8 kPa to 10 kPa or $\text{SaO}_2/\text{SpO}_2$ above 90%.
5. According to ICU population:
 - i) medical;
 - ii) surgical;
 - iii) adults with any respiratory failure;
 - iv) adults with any cerebral disease;
 - v) adults with any heart disease;
 - vi) adults with any trauma;
 - vii) adults with COPD.
6. According to oxygen delivery system:
 - i) invasive mechanical ventilation with endotracheal tube;
 - ii) any non-invasive oxygen administration.

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis for each outcome excluding trials with overall 'high risk of bias'.

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following analyses:

1. 'best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group survived, had no SAE and had no morbidity; and all participants with missing outcomes in the control group did not survive, had an SAE and had morbidity;

2. 'worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group did not survive, had an SAE and had morbidity; and all participants with missing outcomes in the control group did survive, had no SAE and had no morbidity.

We will present results from both scenarios in the review.

To assess the potential impact of the missing data for continuous outcomes, we will perform the two following analyses:

1. 'best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group had mean (from participants with follow-up) + 2 × SD; and all participants with missing outcomes in the control group had mean (from participants with follow-up) - 2 × SD;

2. 'worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group had mean (from participants with follow-up) - 2 × SD; and all participants with missing outcomes in the control group had mean (from participants with follow-up) + 2 × SD ([Jakobsen 2014](#)).

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analyses: where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If there are no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

To assess the potential impact of meta-analysing trials comparing two low targets (FiO₂ below 0.5 or PaO₂ below 10 kPa or SaO₂/SpO₂ below 95%) or two high targets (FiO₂ above 0.5 or PaO₂ above 10 kPa or SaO₂/SpO₂ above 95%), we will perform sensitivity analyses excluding trials comparing two low targets or two high targets.

'Summary of findings' tables

We will use the GRADE system ([Guyatt 2008](#)) to assess the quality of the body of evidence associated with each of the primary outcomes (all-cause mortality, SAEs, quality of life) and secondary outcomes (lung injury, acute myocardial infarction, stroke, sepsis) by constructing 'Summary of findings' tables using the GRADE software ([GRADEpro 2014](#)). For each primary and secondary outcome, first, we will present summaries of findings in RCTs with overall low risk of bias and second, results in all trials.

The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates ([Jakobsen 2014](#)), and risk of publication bias. We will include all risk of bias in the 'Summary of findings' table and then downgrade the quality of the evidence to take the bias into account. However, we do not expect to identify any trials using adequate blinding of participants and personnel due to the practice of administration of oxygen. Hence, we will base our primary conclusions on the results of the analyses of the primary outcomes with low risk of bias in all bias risk domains except 'blinding of participants and personnel' and the TSA-adjusted CIs. The limitations of the expected lack of 'blinding of participants and personnel' for conclusions will be thoroughly discussed in the final review ([Hrobjartsson 2014](#); [Pocock 2015](#)).

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Hyperoxia] explode all trees
- #2 MeSH descriptor: [Anoxia] explode all trees
- #3 MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees
- #4 MeSH descriptor: [Oxygen] explode all trees
- #5 (inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) near3 (oxygen):ti,ab,kw
- #6 (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2):ti,ab,kw
- #7 (#1 or #2 or #3 or #4 or #5 or #6)
- #8 MeSH descriptor: [Critical Illness] explode all trees
- #9 MeSH descriptor: [Critical Care] explode all trees
- #10 MeSH descriptor: [Intensive Care Units] explode all trees
- #11 MeSH descriptor: [Emergency Medicine] explode all trees
- #12 MeSH descriptor: [Emergency Service, Hospital] explode all trees
- #13 (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU*):ti,ab,kw
- #14 MeSH descriptor: [Heart Arrest] explode all trees
- #15 MeSH descriptor: [Myocardial Infarction] explode all trees
- #16 (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct*):ti,ab,kw
- #17 MeSH descriptor: [Shock] explode all trees
- #18 (shock):ti,ab,kw (Word variations have been searched)
- #19 MeSH descriptor: [Cranio cerebral Trauma] explode all trees
- #20 (traumatic brain injury or TBI or head trauma):ti,ab,kw
- #21 MeSH descriptor: [Stroke] explode all trees
- #22 (stroke or intracranial bleeding or intracranial hemorrhage):ti,ab,kw
- #23 MeSH descriptor: [Sepsis] explode all trees
- #24 MeSH descriptor: [Shock, Septic] explode all trees

#25 (sepsis or septic shock):ti,ab,kw

#26 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)

#27 (#7 and #26)

Appendix 2. MEDLINE (OvidSP) search strategy

1. exp Hyperoxia/
2. exp Anoxia/
3. exp Oxygen Inhalation Therapy/
4. exp Oxygen/
5. ((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) adj oxygen).mp.
6. (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Critical Illness/
9. exp Critical Care/
10. exp Intensive Care Units/
11. exp Emergency Medicine/
12. exp Emergency Service, Hospital/
13. (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU*).mp.
14. exp Heart Arrest/
15. exp Myocardial Infarction/
16. (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct*).mp.
17. exp Shock/
18. shock.mp.
19. exp Craniocerebral Trauma/
20. (traumatic brain injury or TBI or head trauma).mp.
21. exp Stroke/
22. (stroke or intracranial bleeding or intracranial hemorrhage).mp.
23. exp Sepsis/
24. exp Shock, Septic/
25. (sepsis or septic shock).mp.
26. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 7 and 26
28. randomized controlled trial.pt.
29. controlled clinical trial.pt.
30. randomized.ab.
31. placebo.ab.
32. clinical trial.sh.
33. randomly.ab.
34. trial.ti.
35. 28 or 29 or 30 or 31 or 32 or 33 or 34
36. humans.sh.
37. 35 and 36
38. 27 and 37

Appendix 3. Embase (OvidSP) search strategy

1. *hyperoxia/
2. *hypoxia/
3. *oxygen therapy/
4. *oxygen/
5. *arterial oxygen saturation/
6. *oxygen blood level/
7. *arterial oxygen tension/
8. *blood oxygen tension/
9. ((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) adj oxygen).tw.
10. (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2).tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. *critical illness/
13. *intensive care/
14. *intensive care unit/
15. *emergency medicine/
16. *emergency health service/
17. (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU*).tw.
18. *heart arrest/
19. *acute heart infarction/
20. (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct*).tw.
21. *shock/
22. shock.tw.
23. *traumatic brain injury/
24. (traumatic brain injury or TBI or head trauma).tw.
25. *cerebrovascular accident/
26. (stroke or intracranial bleeding or intracranial hemorrhage).tw.
27. *sepsis/
28. *septic shock/
29. (sepsis or septic shock).tw.
30. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 11 and 30
32. CROSSOVER PROCEDURE.sh.
33. DOUBLE-BLIND PROCEDURE.sh.
34. SINGLE-BLIND PROCEDURE.sh.
35. (crossover* or cross over*).ti,ab.
36. placebo*.ti,ab.
37. (doubl* adj blind*).ti,ab.
38. allocat*.ti,ab.
39. trial.ti.
40. RANDOMIZED CONTROLLED TRIAL.sh.
41. random*.ti,ab.
42. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
44. 42 not 43
45. 31 and 44

Appendix 4. Science Citation Index - Expanded search strategy

#1 TITLE: (((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) and oxygen))

#2 TITLE: ((hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2))

#3 (#1 OR #2)

#4 TOPIC: ((emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU*))

#5 TOPIC: ((cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct*))

#6 TOPIC: ((shock))

#7 TOPIC: ((traumatic brain injury or TBI or head trauma))

#8 TOPIC: ((stroke or intracranial bleeding or intracranial hemorrhage))

#9 TOPIC: ((sepsis or septic shock))

#10 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)

#11 (#3 AND #10)

#12 TOPIC: ((random* OR control* OR RCT OR placebo OR group* OR trial*))

#13 (#11 AND #12)

Appendix 5. BIOSIS Previews search strategy

#1 TITLE: (((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) and oxygen))

#2 TITLE: ((hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2))

#3 (#1 OR #2)

#4 TOPIC: ((emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU*))

#5 TOPIC: ((cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct*))

#6 TOPIC: ((shock))

#7 TOPIC: ((traumatic brain injury or TBI or head trauma))

#8 TOPIC: ((stroke or intracranial bleeding or intracranial hemorrhage))

#9 TOPIC: ((sepsis or septic shock))

#10 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)

#11 (#3 AND #10)

#12 TOPIC: ((random* OR control* OR RCT OR placebo OR group* OR trial*))

#13 (#11 AND #12)

Appendix 6. CINAHL search strategy

S1 MM hyperoxia

S2 MM anoxia

S3 MM oxygen therapy

S4 MM oxygen

S5 AB ((inspir*) or (inhal*) or (fraction*) or (concentrat*) or (arterial*) or (saturation) or (level*) or (tension*) or (supply*) or (supplement*) or (supplie*) or (therap*) or (administr*) or (dosag*) or (dose*) or (dosing*)) AND AB (oxygen)

S6 AB (hyperoxia) or (hyperoxemia) or (hyperoxaemia) or (hypoxia) or (hypoxemia) or (hypoxaemia) or (anoxia) or (anoxemia) or (anoxaemia) or (arterial oxygen) or (high oxygen) or (oxygenat*) or (blood gas) or (oxygen saturation) or (pao2) or (sao2) or (spo2) or (fio2)

S7 MM critical illness

S8 MM critical care

S9 MM intensive care units

S10 MM emergency medicine
 S11 AB (emergency department*) or (ED) or (emergency room*) or (ER) or (high dependency unit*) or (HDU) or (prehospital*) or (critically ill) or (acutely ill) or (intensive care) or (critical care) or (ICU*)
 S12 MM heart arrest
 S13 MM myocardial infarction
 S14 AB (cardiac arrest) or (cardiac failure) or (CPR) or (heart arrest) or (heart failure) or (myocardial infarct*)
 S15 MM shock
 S16 AB (shock)
 S17 AB (traumatic brain injury) or (TBI) or (head trauma)
 S18 MM stroke
 S19 AB (stroke) or (intracranial bleeding) or (intracranial hemorrhage)
 S20 MM sepsis
 S21 AB (sepsis) or (septic shock)
 S22 (S1 OR S2 OR S3 OR S4 OR S5 OR S6)
 S23 (S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21)
 S24 (MH "Clinical Trials+")
 S25 PT Clinical trial
 S26 TX clinic* n1 trial*
 S27 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
 S28 TX randomi* control* trial*
 S29 (MH "Random Assignment")
 S30 TX random* allocat*
 S31 TX placebo*
 S32 (MH "Placebos")
 S33 (MH "Quantitative Studies")
 S34 TX allocat* random*
 S35 (S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34)
 S36 (S22 AND S23 AND S35)

Appendix 7. AMED search strategy

S1 TX ((inspir*) or (inhal*) or (fraction*) or (concentrat*) or (arterial*) or (saturation) or (level*) or (tension*) or (supply*) or (supplement*) or (supplie*) or (therap*) or (administr*) or (dosag*) or (dose*) or (dosing*)) AND AB (oxygen)
 S2 TX (hyperoxia) or (hyperoxemia) or (hyperoxaemia) or (hypoxia) or (hypoxemia) or (hypoxaemia) or (anoxia) or (anoxemia) or (anoxaemia) or (arterial oxygen) or (high oxygen) or (oxygenat*) or (blood gas) or (oxygen saturation) or (pao2) or (sao2) or (spo2) or (fio2)
 S3 TX (emergency department*) or (ED) or (emergency room*) or (ER) or (high dependency unit*) or (HDU) or (prehospital*) or (critically ill) or (acutely ill) or (intensive care) or (critical care) or (ICU*)
 S4 TX (cardiac arrest) or (cardiac failure) or (CPR) or (heart arrest) or (heart failure) or (myocardial infarct*)
 S5 TX (shock)
 S6 TX (traumatic brain injury) or (TBI) or (head trauma)
 S7 TX (stroke) or (intracranial bleeding) or (intracranial hemorrhage)
 S8 TX (sepsis) or (septic shock)
 S9 TX (random* OR control* OR RCT OR placebo OR group* OR trial*)
 S10 (S1 OR S2)
 S11 (S3 OR S4 OR S5 OR S6 OR S7 OR S8)
 S12 (S9 AND S10 AND S11)

Appendix 8. LILACS search strategy

("oxygen" or "oxygenation" or "saturation" or "hyperoxia" or "hyperoxemia" or "hyperoxaemia" or "hypoxia" or "hypoxemia" or "hypoxaemia" or "anoxia" or "anoxemia" or "anoxaemia" or "blood gas" or "pao2" or "sao2" or "spo2" or "fio2") AND ("emergency department" or "ED" or "emergency room" or "ER" or "high dependency unit" or "HDU" or "prehospital" or "critically ill" or "acutely ill" or "intensive care" or "critical care" or "ICU" or "cardiac arrest" or "cardiac failure" or "CPR" or "heart arrest" or "heart failure" or "myocardial infarction" or "shock" or "traumatic brain injury" or "TBI" or "head trauma" or "stroke" or "intracranial bleeding" or "intracranial hemorrhage" or "sepsis" or "septic shock") AND ((PT:"randomized controlled trial" OR PT:"controlled clinical trial" OR PT:"multicenter study" OR MH:"randomized controlled trials as topic" OR MH:"controlled clinical trials as topic" OR MH:"multicenter study as topic" OR MH:"random allocation" OR MH:"double-blind method" OR MH:"single-blind method") OR ((ensaio\$ OR ensayo\$ OR trial\$) AND (azar OR acaso OR placebo OR control\$ OR aleat\$ OR random\$ OR enmascarado\$ OR simpleciego OR ((simple\$ OR single OR duplo\$ OR doble\$ OR double\$) AND (cego OR ciego OR blind OR mask))) AND clinic\$)) AND NOT (MH:animals OR MH:rabbits OR MH:rats OR MH:primates OR MH:dogs OR MH:cats OR MH:swine OR PT:"in vitro")

Appendix 9. Data collection form

TRIAL IDENTIFICATION		
Author and year		
Publication type	Lead trial:	Secondary publ.: Name of primary publication of the same trial

STUDY ELIGIBILITY											
RCT			Relevant participants			Relevant intervention			Relevant outcomes		
Yes	No	Unclear	Yes	No	Unclear	Yes	No	Unclear	Yes	No*	Unclear

*Issue relates to selective reporting when study authors may have taken measurements for particular outcomes but did not report these within the paper(s). Review authors should contact trialists for information on possible non-reported outcomes and reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should be excluded.

DO NOT PROCEED IF ANY OF THE ABOVE ANSWERS IS 'NO'

Include	Exclude
	Record reason for exclusion, which is to be inserted into the 'Table of excluded studies'

PARTICIPANTS	
Eligibility	How was participant eligibility defined?
Age (mean, median, range, etc.)	
Sex of participants (numbers/%, etc.)	
Disease status/type, etc. (if applicable)	
Notes	

INTERVENTIONS	
Experimental intervention	Describe experimental intervention (incl. oxygenation target, oxygen administration system, duration)
Control intervention	Describe control intervention (incl. oxygenation target, oxygen administration system, duration)
Co-interventions (any intervention given equally in both interventions)	Specify any other co-interventions

OTHER TRIAL INFORMATION	
Aim of trial	
Country/Countries	
Trial design (parallel/cross-over, single centre/multicentre)	
Trial duration (intervention and follow-up)	Weeks, months, years, not stated
Definition of hypoxaemia, normoxaemia and hyperoxaemia by trialist	Hypoxaemia: Normoxaemia: Hyperoxaemia:
The trial included only participants admitted to ICU?	
Which targets did the participants actually achieve?	

(Continued)

Withdrawals	Were these described?
Study funding source (Incl. role of funders)	
Possible conflicts of interest (for study authors)	
Other	
Notes	

RISK OF BIAS ASSESSMENT

L: low risk of bias, U: unclear risk of bias, H: high risk of bias

Random sequence generation	
<p>Low risk: if sequence generation is achieved using computer, random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards and throwing dice are also adequate if performed by an independent adjudicator</p> <p>Unclear risk: if the method of randomization is not specified.</p> <p>High risk: if the allocation sequence is not random.</p>	<p>Grade L / U / H</p>
Support for judgement	

Allocation sequence concealment*	
<p>Low risk: if the allocation of participants is performed by a central independent unit, on-site locked computer, identically looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent investigator. There must be no risk of the investigator knowing the sequence</p> <p>Unclear risk: if the trial is classified as randomized but the allocation concealment process is not described</p> <p>High risk: if the allocation sequence is known to the investigators who assigned participants</p>	<p>Grade L / U / H</p>
Support for judgement	

*Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding

Blinding of participants and personnel	
Person responsible for participant care	Yes / No
Participant	Yes / No
Outcome assessor	Yes / No
Other (please specify)	Yes / No
<p>Low risk: if the participants and the personnel are blinded to treatment allocation and this is described</p> <p>Unclear risk: if the procedure of blinding is insufficiently described or not described at all</p> <p>High risk: if blinding of participants and personnel is not performed</p>	<p>Grade L / U / H</p>
Support for judgement	

Blinding of outcome assessment	
<p>Low risk: if the trial investigators performing the outcome assessments, analyses and calculations are blinded to the intervention</p> <p>Unclear risk: if the procedure of blinding is insufficiently described or not described at all</p> <p>High risk: if blinding of outcome assessment is not performed.</p>	<p>Grade L / U / H</p>
Support for judgement	

Incomplete outcome data	
<p>Low risk: there are no dropouts or withdrawals for all outcomes, or the numbers and reasons for the withdrawals and dropouts for all outcomes are clearly stated and can be described as being similar in both groups</p> <p>As a general rule the trial is judged as at a low risk of bias due to incomplete outcome data if the number of dropouts is less than 5%. However, the 5% cut-off is not definitive.</p> <p>Unclear risk: the numbers and reasons for withdrawals and dropouts are not clearly stated.</p> <p>High risk: the pattern of dropouts can be described as being different in the two intervention groups or the trial uses improper methodology in dealing with the missing data, e.g. last observation carried forward</p>	<p>Grade L / U / H</p>

(Continued)

Support for judgement	
Selective outcome reporting	
Low risk: a protocol is published before or at the time the trial is begun and the outcome called for in the protocol is reported on. Unclear risk: if there is no protocol and the outcome is not reported on. High risk: if the outcomes which are called on in a protocol are not reported on	Grade L / U / H
Support for judgement	
Baseline imbalance	
Low risk: no baseline imbalance in important characteristics was noted Unclear risk: baseline characteristics were not reported. High risk: baseline imbalance was due to chance or was due to imbalanced exclusion after randomization	Grade L / U / H
Support for judgement	
Early stopping	
Low risk: sample size calculation was reported and the trial was not stopped, or if the trial was stopped early by formal stopping rules at a point at which the likelihood of observing an extreme intervention effect due to chance was low Unclear risk: sample size calculation was not reported, and if it is not clear whether or not the trial was stopped early High risk: the trial was stopped early because of informal stopping rules, or if the trial was stopped early by a formal stopping rule at a point at which the likelihood of observing an extreme intervention effect due to chance was high	Grade L / U / H
Support for judgement	

Other bias risk	
<p>Low risk: the trial appears to be free of other components (e.g. academic bias or for-profit bias) that could put it at risk of bias</p> <p>Unclear risk: the trial may or may not be free of other components that could put it at risk of bias</p> <p>High risk: there are other factors in the trial that could put it at risk of bias (e.g. authors have conducted trials on the same topic, for-profit bias, etc.)</p>	<p>Grade L / U / H</p>
Support for judgement	

Overall risk of bias	
<p>Low risk: each outcome result will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as low risk of bias</p> <p>High risk: the outcome result will be classified 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'</p> <p>In addition, if one or more of the bias domains described in the above paragraphs are classified as 'unclear' or at 'high risk of bias'</p>	<p>Grade L / H</p>
Support for judgement	

OUTCOMES

PRIMARY OUTCOMES	Available for the trial
All-cause mortality	Yes / No
Number of participants with one or more serious adverse events (dichotomous outcome)	Yes / No
Quality of life	Yes / No

*We used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event ([ICH-GCP 1997](#)), that is, any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity. We will consider all other adverse events as non-serious.

SECONDARY OUTCOMES	Available for the trial
Lung injury*	Yes / No
Acute myocardial infarction**	Yes / No
Stroke**	Yes / No
Severe sepsis**	Yes / No

* Diagnosed after randomization (composite outcome) defined as either ARDS, lung fibrosis, or pulmonary embolism.

** Diagnosed after randomization.

OTHER OUTCOMES OF THE TRIAL	
Additional outcomes	List additional reported outcomes

SUBGROUPS	
Overall risk of bias	High risk of bias Low or uncertain risk of bias
According to ICU population	Medical Surgical
According to different definitions of oxygen target	Oxygen level measured using FiO ₂ Oxygen level measured using PaO ₂ Oxygen level measured using SaO ₂ or SpO ₂ Oxygen level measured using PaO ₂ or SaO ₂ or SpO ₂
According to oxygen delivery system	Invasive mechanical ventilation with endotracheal tube Any non-invasive ventilation

OUTCOMES		
Follow-up periods	List all follow-up periods given in report	
Total no. of randomized participants	Participants in experimental group	Participants in control group

(Continued)

Primary outcomes						
(dichotomous 'end point' outcome)		Participants analysed		Number of events in the groups: E = experimental C = control		Bias of the outcome
All-cause mortality	Maximum follow-up	E (n)	E (n)	E (n)	L / U / H	
		C (n)	C (n)	C (n)		
	End of trial intervention period	E (n)	E (n)	E (n)	L / U / H	
		C (n)	C (n)	C (n)		
Serious adverse events: Nb. Number of counts. If SAE is reported, list them	Maximum follow-up	E (n)	E (n)	E (n)	L / U / H	
		C (n)	C (n)	C (n)		
	End of trial intervention period	E (n)	E (n)	E (n)	L / U / H	
		C (n)	C (n)	C (n)		
(continuous outcome)		Participants analysed	Mean (endpoint or change)	SD	Bias of the outcome	
Quality of life: Type of QoL scale:	Maximum follow-up	E (n)	E	E	L / U / H	
		C (n)	C	C	L / U / H	
	End of trial intervention period	E (n)	E	E	L / U / H	
		C (n)	C	C	L / U / H	

Secondary outcomes				
(dichotomous outcome)		Participants analysed	Number of events in the groups: E = experimental C = control	Bias of the outcome
All-cause mortality	Maximum follow-up	E (n)	E (n)	L / U / H
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	

(Continued)

Acute myocardial infarction	Maximum follow-up	E (n)	E (n)	L / U / H
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	

OTHER INFORMATION

Key conclusion of study authors as stated in paper

Information relevant to the results
Indicate if any data were obtained from the primary author; if results were estimated from graphs, etc. or were calculated by you using a formula (should be stated and the formula given). In general, if results not reported in paper(s) are not obtained, this should be made clear here to be cited in the review

Appendix 10. Criteria for risk of bias evaluation

Random sequence generation

- Low risk: if sequence generation is achieved using computer, random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards and throwing dice are also adequate if performed by an independent adjudicator.
- Unclear risk: if the method of randomization is not specified.
- High risk: if the allocation sequence is not random.

Allocation sequence concealment

- Low risk: if the allocation of participants is performed by a central independent unit, on-site locked computer, identically looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent investigator. There must be no risk of the investigator knowing the sequence.

- Unclear risk: if the trial is classified as randomized but the allocation concealment process is not described.
- High risk: if the allocation sequence is known to the investigators who assigned participants.

Blinding of participants and personnel

- Low risk: if the participants and personnel are blinded to treatment allocation and this is described.
- Unclear risk: if the procedure of blinding is insufficiently described or not described at all.
- High risk: if blinding of participants and personnel is not performed.

Blinding of outcome assessment

- Low risk: if the trial investigators performing the outcome assessments, analyses and calculations are blinded to the intervention.
- Unclear risk: if the procedure of blinding is insufficiently described or not described at all.
- High risk: if blinding of outcome assessment is not performed.

Incomplete outcome data

- Low risk: there are no dropouts or withdrawals for all outcomes, or the numbers and reasons for the withdrawals and dropouts for all outcomes are clearly stated and can be described as being similar in both groups. As a general rule the trial is judged as at a low risk of bias due to incomplete outcome data if the number of dropouts is less than 5%. However, the 5% cut-off is not definitive.

- Unclear risk: the numbers and reasons for withdrawals and dropouts are not clearly stated.
- High risk: the pattern of dropouts can be described as being different in the two intervention groups or the trial uses improper methodology in dealing with the missing data, e.g. last observation carried forward.

Selective outcome reporting

- Low risk: a protocol is published before or at the time the trial is begun and the outcome called for in the protocol is reported on.
- Unclear risk: if there is no protocol and the outcome is not reported on.
- High risk: if the outcomes which are called on in a protocol are not reported on.

Other bias risk

- Low risk: the trial appears to be free of other components (e.g. academic bias or for-profit bias) that could put it at risk of bias.
- Unclear risk: the trial may or may not be free of other components that could put it at risk of bias.
- High risk: there are other factors in the trial that could put it at risk of bias (e.g. authors have conducted trials on the same topic, for-profit bias, etc.)

Overall risk of bias

We will classify all trials as:

- Low risk: the trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as low risk of bias.

- High risk: the trial will be classified 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.

WHAT'S NEW

Date	Event	Description
20 September 2017	Amended	We have cited the systematic review Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients (Gilbert-Kawai 2014).

CONTRIBUTIONS OF AUTHORS

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Performing search strategies: MB.

Writing the protocol: MB, OS, JJ, CM, RD, BR, AP, JW.

Person responsible for reading and checking the protocol before submission: MB.

DECLARATIONS OF INTEREST

Marija Barbateskovic: PhD student at the Centre for Research in Intensive Care and Copenhagen Trial Unit. The PhD is funded by the Innovation Fund Denmark; which is a public fund.

Olav L Schjørring: PhD student at the Centre for Research in Intensive Care and Aalborg University Hospital. The PhD is funded by the Innovation Fund Denmark; which is a public fund. Dr Schjørring is the co-ordination investigator of the HOT-ICU (Handling Oxygenation Targets in the Intensive Care Unit) trial investigating higher versus lower oxygenation targets in patients admitted to the ICU.

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Christian S Meyhoff: Head of Research at Department of Anaesthesiology and Intensive Care Medicine, Bispebjerg and Frederiksberg Hospital. The department directly and indirectly receives research funding from Ferring Pharmaceuticals and Boehringer Ingelheim. CM was the principal investigator of the PROXI trial (Perioperative OXYgen fraction) investigating higher versus lower concentrations of perioperative inspiratory oxygen ([Meyhoff 2009](#)). Furthermore, he is a principle investigator of the [HOT-ICU](#) trial.

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Jørn Wetterslev: member of the Copenhagen Trial Unit task force for developing TSA theory, manual and software and he was also an investigator in the PROXI trial of higher versus lower concentrations of perioperative inspiratory oxygen ([Meyhoff 2009](#)). Furthermore, Dr Wetterslev is a member of the steering group of the [HOT-ICU](#) trial.