BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064047
Article Type:	Protocol
Date Submitted by the Author:	25-Apr-2022
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Keywords:	Adult anaesthesia < ANAESTHETICS, Adult intensive & critical care < ANAESTHETICS, TRAUMA MANAGEMENT, Respiratory physiology < THORACIC MEDICINE

Comparing Restrictive vs. Liberal Oxygen Strategies for Trauma Patients: The TRAUMOX2 Trial

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ABSTRACT

Introduction: Supplemental oxygen is commonly used in trauma patients, although it may lead to hyperoxaemia that has been associated with pulmonary complications and increased mortality. The primary objective of this trial, TRAUMOX2, is to compare a restrictive versus a liberal oxygen strategy the first eight hours following trauma.

Methods and Analysis: TRAUMOX2 is an investigator-initiated, international, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial.
Adult patients with suspected major trauma are included and randomised to eight hours of a restrictive or liberal oxygen strategy. The restrictive group receives the lowest dosage of oxygen (≥21%) that ensures an SpO_2 of 94%. The liberal group receives 12-15 L O_2/min or FiO_2=0.6-1.0.
The primary outcome is mortality and/or major respiratory complications (pneumonia and/or ARDS) within 30 days (composite outcome).
With 710 participants in each arm we will be able to detect a 33% risk reduction with a restrictive oxygen strategy if the incidence of our primary outcome is 15% in the liberal group.

Ethics and dissemination: TRAUMOX2 is carried out in accordance with the Helsinki II Declaration. It has been approved by the Danish Committee on Health Research Ethics for the Capital Region (H-21018062) and The Danish Medicines Agency, as well as the Dutch Medical Research Ethics Committee Erasmus MS (NL79921.078.21 and MEC-2021-0932). A website (www.traumox2.org) is available for updates and the study results will be published in an international peer-reviewed scientific journal.

Strengths and limitations

- TRAUMOX2 will provide high-level evidence on the use of supplemental oxygen for trauma patients
- Although the arterial oxygen tension is a more accurate measure of tissue exposure to oxygen, the intervention in TRAUMOX2 is based on inspiratory oxygen fraction to ensure feasibility in the acute care setting and detect pulmonary oxygen toxicity

Registration details: European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) (2021-000556-19); www.clinicaltrials.gov. (NCT05146700)

INTRODUCTION

BACKGROUND AND RATIONALE

In trauma resuscitation supplemental oxygen is often administered to treat or prevent hypoxaemia as recommended by the Advanced Trauma Life Support manual.[1] This guideline does not have a specific therapeutic goal. Oxygen is administered in many other situations too, sometimes in a non-consistent manner[2–4] and very often without even being prescribed.[5] In a recent systematic review our group found the evidence for the use of supplemental oxygen in the trauma population to be sparse.[6] Nevertheless, in a large retrospective study on 864,340 trauma patients a propensity score matching analysis showed the administration of supplemental oxygen was associated with a significantly increased risk of in-hospital mortality and acute respiratory distress syndrome (ARDS).[7] Furthermore, a recent systematic review and meta-analysis comparing liberal versus restrictive oxygen strategy for a broad mix of acutely ill medical and surgical patients found an association between liberal oxygen administration and increased mortality.[8] Of note, only one small study on trauma patients (patients with traumatic brain injury), which did not report mortality data, was included. Conversely this study showed that degree of disability was significantly reduced at six months in the group receiving liberal compared to restrictive oxygen.[9]

Hyperoxaemia is a common finding in trauma patients[5,10] and in mechanically ventilated patients in general.[11,12] However, in the Intensive Care Unit (ICU) and in surgical patients hyperoxaemia has been associated with major pulmonary complications.[13,14] For example, a recent retrospective study found hyperoxaemia to be an independent risk factor for ventilator associated pneumonia .[14] Nevertheless, a highly debated recommendation from the World Health Organisation states that adult patients undergoing general anaesthesia for surgical procedures should receive an FiO_2 of 80% intraoperatively as well as in the immediate postoperative period for two to six hours to reduce the risk of surgical site infection.[15] A randomised study, however, found no difference in the risk of surgical site infection according to FiO_2 concentration intraoperatively.[16] Furthermore, a study on 152,000 mechanically ventilated patients found no association between hyperoxia and mortality during the first 24 hours in the ICU,[17] and another study on 14,000 mixed ICU patients found that a PaO_2 of approximately 18 kPa resulted in the lowest mortality.[18] Finally, a recent study randomised 2928 ICU patients to either low or high arterial oxygen tension target (defined as 8 vs 12 kPa), for a maximum of 90 days and found no difference in mortality.[19]

Therefore, whether the trauma population could benefit from a more restrictive supplemental oxygen approach than recommended by current international trauma guidelines presents a large and important knowledge gap. In a recent pilot randomised clinical trial (*TRAUMOX1*[20]*,* Clinicaltrials.gov Registration number: NCT03491644*)* we compared a restrictive and a liberal oxygen strategy for 24 hours after trauma (N=41) and found maintenance of normoxaemia following trauma using a restrictive oxygen strategy to be feasible. The study served as the basis for the following larger clinical trial; TRAUMOX2.

In TRAUMOX2 we hypothesize that a restrictive compared to a liberal oxygen strategy for eight hours following trauma will result in a lower rate of 30-day mortality and/or major respiratory complications (pneumonia and/or ARDS) (combined endpoint).

METHODS

Study setting

The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.[21] The SPIRIT 2013 checklist is presented in Appendix 1.

TRAUMOX2 is an investigator-initiated, international, multicentre, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial.

Participating trauma centres must be able to provide definitive treatment of trauma patients (tertiary care i.e. no transfer to more specialized institution needed), possess a trauma registry, and have an average of approximately 400 trauma patients per year. All trauma centres must be within the EU and thus the EU Clinical Trial Regulation are applied. A complete list of the study sites can be viewed on the trial website (www.traumox2.org).

Eligibility criteria

Patients aged 18 years or older, including fertile women, are included. Participants must have undergone blunt or penetrating trauma, be directly transferred from the scene of accident to one of the participating trauma centres and trigger trauma team activation (no secondary transfers from other hospitals). Moreover, the including physician must initially expect a hospital length of stay for 24 hours or longer. Patients with no/minor injuries after secondary survey are excluded if they are expected to be discharged within 24 hours to ensure only patients with a substantial trauma are included. Patients in cardiac arrest before or on admission and patients with a suspicion of carbon monoxide intoxication are excluded.

Interventions

Participants are randomised to eight hours of either restrictive or liberal supplemental oxygen treatment. The restrictive group receives the lowest dosage of oxygen (≥21%) that ensures an arterial oxyhaemoglobin saturation (SpO_2) target of 94% either using no supplemental oxygen, a nasal cannula, a non-rebreather mask, or mechanical ventilation (intubated patients). Thus, only trial participants without a need for supplemental oxygen to maintain an SpO_2 ≥94% can saturate above 94%. The liberal group receives 15 L O_2/min via a non-rebreather mask for non-intubated trial participants and an FiO_2=1.0 for intubated trial patients in the prehospital setting, in the trauma bay and during intrahospital transportation. In the operating room, ICU, post-anaesthesia care unit and ward the flow/ FiO_2 may be reduced to 12 L O_2/min/FiO_2=0.6 if the arterial oxygen saturation ≥98%. In both groups, pre-oxygenation should be done prior to intubation.

Outcomes

The primary outcome is the incidence of 30-day mortality and/or major respiratory complications (pneumonia and/or ARDS) (composite outcome). Secondary outcomes include mortality at 30 days and 12 months post trauma, major respiratory complications (pneumonia and acute respiratory distress syndrome) within 30 days, hospital length of stay (HOS LOS), ICU length of stay (ICU LOS), days alive outside the ICU, time on mechanical ventilation (until 30 days), days alive without mechanical ventilation, re-intubation within 30 days, pneumonia post-discharge, surgical site infections within 30 days, episodes with hypoxaemia during intervention (SpO_2 <90%), and EQ-5D-5L score at six and 12 months post trauma, and Glasgow Outcome Scale-Extended (GOSE) at six and 12 months post trauma. The EQ-5D-5L score is a widely used generic measure for health-related quality of life, and [22] GOSE assesses physical and mental consequences of traumatic brain injury.[23]

Randomisation

Patients are randomised 1:1 in variable block sizes and stratified by centre (prehospital base or trauma centre) and tracheal intubation at inclusion. The randomisation table is generated outside of REDCap by a statistician otherwise not affiliated with the study. The allocation sequence list and block size are only known by the statistician and will remain concealed from the investigators. Prior to randomisation, a proxy consent must be obtained (or according to legislation in each country). Afterwards, randomisation is determined by opening a concealed envelope with information on allocation. The envelopes are available both pre- and in-hospital. Each concealed envelope contains a study ID that matches a study ID on the randomisation list generated by the statistician.

Participant timeline

Please see figure 1.

Blinding

The study outcome assessor- and analyst-blinded with regards to treatment: treating staff are aware of the trial participants' randomisation group. However, at least two allocation blinded primary outcome assessors (specialists in anaesthesia, intensive care, emergency medicine or similar) are appointed in each country to assess in-hospital lung complications (pneumonia and/or ARDS). Blinding is ensured by concealing all information indicative of the allocation prior to assessment.
The statistician and manuscript writers will be blinded towards the allocation of treatment once the trial ends when data is being analysed and the manuscript is drafted.

Recruitment and assignment of interventions

Depending on the possibilities of the recruiting site, patients are randomised and included either in the prehospital phase or in the trauma bay:

Prehospital phase (optional)

As soon as possible and after immediate and necessary life-saving procedures have been performed, a prehospital emergency physician (the including physician) assesses a patient eligible for inclusion. If all inclusion criteria are met, the including physician obtains proxy consent through a legally appointed study guardian (physician) by telephone. Proxy consent before inclusion may not be necessary in all participating countries. National rules and laws are followed in the specific country on both proxy consent as well as trial participant/trial participant's next-of-kin consent in general. Once the trauma patient is included, the including physician randomises the trial participant to the intervention (restrictive oxygen strategy) or control (liberal oxygen strategy) group by opening a concealed envelope with information on the allocation. The including physician registers the trial participant in an electronic database. If the trial participant is transported by helicopter, it is advised to fly at the lowest reasonable altitude to reduce the alterations from normal atmospheric oxygen tension at sea level. Treatment is initiated and continued for eight hours after enrolment. Time of initiation equals T0 (see figure 1).

Trauma bay

As soon as possible or after immediate and necessary life-saving procedures have been performed the including physician (e.g. the trauma leader or an attending anaesthesiologist) judges whether the patient is eligible for the study. If eligible, the including physician obtains proxy consent through a legally appointed study guardian (physician). Proxy consent before inclusion may not be necessary in all participating countries. National law is followed in the specific country on both proxy consent as well as trial participant/trial participant's next-of-kin consent in general. Once the trauma patient is included, the including physician randomises the trial participant to the intervention

(restrictive oxygen strategy) or control (liberal oxygen strategy) group by opening a concealed envelope with information on allocation. The including physician registers the trial participant in an electronic database. Treatment is initiated and continued for eight hours after enrolment. Time of initiation equals T0 (see figure 1) and must not be delayed more than 90 minutes after hospital arrival.

Consent

Consent procedures vary according to including location. In broad terms, the patients eligible for inclusion in the trial are temporarily incompetent because of the acute and severe condition related to their traumatic injuries. The trauma patients are eligible either on the scene of accident or upon arrival in the trauma bay where early resuscitation with the use of multiple interventions and even surgery may be necessary. Symptoms include severe pain, impaired consciousness, and early complications are circulatory and respiratory failure requiring emergency intubation. Some of these trial participants are expected to die. The intervention tested in this trial is pivotal to be given immediately in the early phase of resuscitation. In clinical trials aiming to improve treatment of traumatic injuries it is necessary to include unconscious and incompetent patients as no clinically relevant animal model exists. As soon as possible, local consent procedures are followed. In Denmark, proxy consent is first obtained through a legally appointed study guardian. Hereafter, consent is sought by the trial participants' next-of-kin as soon as-possible, and when possible, consent is sought by the trial participant. If the trial participant is not able to consent within 30 days, consent from the next-of kin is accepted as the final consent. If the next-of-kin is unavailable, a secondary proxy consent can be obtained through a legally appointed study guardian, and this can also be accepted as the final consent. Detailed consent procedures in specific locations can be found on the trial website.

Data collection methods, registration, and monitoring

Oxygen dosages and saturations are recorded every hour and two arterial blood gas analyses are obtained and noted in a paper data collection sheet specifically made for this study ("Randomisation, data collection sheet and REDCap inclusion", available on the study website). Further data collection is obtained by accessing the trial participants' medical records. Data points include trial participant characteristics (name, unique patient identifier, age, sex, height, weight), prehospital data (vital signs, trauma mechanism, details on supplemental oxygen in the prehospital phase (indication, SpO_2, supplemental oxygen yes/no, intubation yes/no, oxygen flow/FiO_2), Injury Severity Score, complete list of injuries, transportation mode to the trauma bay), time points (date and time of trauma, on-scene arrival and departure, trauma bay arrival, ICU/ward arrival, time of intubation/extubation/re-intubation for intubated trial participants, time of surgery, duration of surgery), hospital and ICU length of stay, vital signs on arrival to the trauma bay (including arterial blood gas analysis if available), in-hospital variables (pneumonia, ARDS, other infections (surgical site infection or sepsis)), ischaemic events within 7 days after admission (myocardial infarction or cerebral ischemia), Adverse Events and Serious Adverse Events (SAE), co-morbidities prior to trauma (categorised in heart disease, lung disease, other diseases), active smoker (yes/no), specifics of possible brain injury (type and extent) and other cerebral complications, and time until of death.

Trial participants with traumatic brain injury admitted to a neurosurgical intensive care unit can be monitored according to standard practice in the local facility. It is acceptable, but optional, to perform continuous intraparenchymal brain oxygen measurements.

For all TRAUMOX2 trial participants it is possible to deviate from the protocol if clinically justified by the treating physician. Such deviations should always be documented including the clinical justification.

Mortality status is collected through local registries or according to local practice. EQ-5D-5L and GOSE score are collected through telephone interviews, either with the trial participant or with the trial participant's next-of-kin or

caregiver. Possible pneumonia post-discharge is evaluated through medicines prescribed after hospital discharge in countries where this information is available.

All trial participants will have two arterial blood gasses (ABGs) drawn within the intervention period. The first ABG is drawn at hour 1 ± 30 minutes (T1) after randomisation (initiation of intervention is considered hour 0). If an ABG is not obtainable at hour 1 due to still being prehospital or other circumstances, the ABG must be obtained as soon as possible. The second ABG is drawn at hour 6 ± 2 hours (T6). If more than two ABGs are collected during the intervention (ABGs not related to the study), the ABGs closest to the specified time slots (T1 and T6) should be used for data entry.

Furthermore, the trial participant or his/her next-of-kin is asked for an additional and separate consent form, not directly related to this research project, to have their blood stored in a biobank established for future research. It is optional whether the participating centres contribute to the biobank.

Data is stored in an electronic, web-based, secure, centralised, user-friendly interface using a data collection sheet in REDCap[24] specifically made for this trial. This data management system is secure, fully compliant with all regulatory guidelines and a complete audit-trail for data entry validation. Trained members of the research team are responsible for data collection and entry into REDCap using local electronic clinical registries. Therefore, the electronic case report form (eCRF) is digital. In case of system malfunction, a paper version of the data collection sheet is available. The REDCap database is set up from Rigshospitalet in the Capital Region in Denmark and participating centres are invited to data entry in this database.

External monitoring of registered data is applied at all trial centres.

Definitions

Pneumonia is defined as per the CDC criteria[25].

ARDS is defined as per the Berlin definition[26].

Traumatic brain injury is defined as[27]:

- Severe: AIS ≥5
- Moderate: AIS 3–4
- Mild: AIS 1–2

Please see figure 2 for a detailed description of pneumonia and ARDS.

Statistical Analysis

In larger studies, mortality from trauma has been estimated to be around 6-12%,[28] and the incidence of ventilator associated pneumonia post trauma to be almost 30%.[14] With 710 trial participants in each arm, we will be able to detect a 33% risk reduction with a restrictive supplemental oxygen strategy (with 80% power at the 5% significance level) if the incidence of our primary outcome is 15% in the liberal group. Our primary analysis will be a modified intention-to-treat analysis, but a per-protocol analysis will also be carried out. A detailed statistical analysis plan, including the pre-specified subgroup analyses, will be made. In the primary analysis, we will exclude trial participants where no injuries are found, defined as Injury Severity Score=0.

If less than 5% of data required for any specific analysis on primary or secondary outcomes are missing, a complete case analysis will be performed. If more than 5% are missing, and it is concluded that data are not 'missing completely at random' inverse probability weighting will be used to correct possible bias.[29] A sensitivity analysis on the assumptions used for missing data will be done to verify robustness.

Inclusion of trial participants will end when the goal of 1420 evaluable trial participants has been reached including the 30-day follow up period. This means that the maximum number of trial participants will be 1600 as inclusion will continue during evaluation of the 30-day follow-up. EQ-5D-5L score and GOSE score at six months and 12 months will be obtained. Mortality at 30 days and 12 months will also be obtained. The primary composite outcome will be compared between the two groups using logistic regression reported as Odds Ratio with 95% CI. The primary analysis will be adjusted for age, sex, centre, intubated at randomisation (yes/no), and known pneumonia on admission (under treatment). Secondary outcomes will also be compared between the two groups using logistic regression for dichotomous data and linear regression for continuously valued outcomes. We will use a 5% significance level. Any changes or additional analyses will be reported.

In the per-protocol analysis, all trial participants with ≥1 major protocol violation will be removed.

Specified subgroup analyses will be made on trial participants initially intubated (within one hour of the accident) (yes/no), trial participants with ICU admission (yes/no), trial participants with moderate and severe traumatic brain injuries (yes/no), trial participants with chronic pulmonary disease (yes/no), registered episodes with hypoxaemia as well as an analysis on trial participants enrolled prehospital versus in-hospital. An analysis adjusted for Injury Severity Score will also be conducted.

The statistical analysis will be performed by a statistician.

Adverse and serious adverse events

To monitor adverse events a TRAUMOX2 investigator assesses the trial participant's medical record once within the first 24 hours and every third day until discharge (maximum of 30 days).

This group of trial participants are expected to have a lot of complications. It is the established practice in trials on critically ill patients that adverse events are part of the natural trajectory of the primary disease process or expected complications of the critical illness.[30] Therefore, we have chosen to record only the occurrence of atelectasis and irritability of airway mucosa.

All SAEs are registered. The registration is done in REDCap and once a SAE registration is complete, the sponsor and coordinating investigator receives an e-mail notification immediately via the REDCap notification e-mail system.

Ethics and dissemination

Trial participant insurances are in place at all trial sites either through the national health insurance or through specifically supplied local trial insurances as required according to the specific trial sites and national regulations.

This RCT is carried out in accordance with the principles from the Helsinki II Declaration in its latest version.[31] The protocol has been approved by the Danish Committee on Health Research Ethics for the Capital Region of Denmark (H-21018062) and The Danish Medicines Agency, as well as the Dutch Medical Research Ethics Committee Erasmus MS (NL79921.078.21 and MEC-2021-0932). It is monitored by the regional Good Clinical Practice Unit. Data management must be approved according to national legislation. Furthermore, the trial has been registered in the

European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) (2021-000556-19) as well as on www.clinicaltrials.gov (NCT05146700).

Finally, a website (www.traumox2.org) is available for further information and updates on the trial.

Oxygen is a well-known drug given in a dosage of FiO_2 0.21-1.0 and can be administered by paramedics, nurses, and doctors. The side-effects of normobaric oxygen-strategies include slightly decreased heart rate as well as increased risk of atelectasis, pleuritis and respiratory distress syndrome. The greater the FiO_2, the greater the risk. As the standard treatment of care currently includes high levels of FiO_2, it seems plausible that the intervention group will have a decreased risk for developing these side-effects.

On the other side, hypoxia is documented to be deleterious. To avoid the risk of hypoxia, all trial participants are monitored with continuous pulse oximetry (documented/registered every hour) and arterial blood gases to avoid desaturation. If the saturation is unmeasurable due to e.g. hypovolemia or hypothermia the treating physician will decide and document the treatment of choice. When measurable again, the allocated intervention will resume. In the TRAUMOX1 trial we observed seven episodes of desaturation (SpO_2 below 90%) in the restrictive group (median 87% [87-89]). Of note, five of the seven cases of SpO_2 below 89% occurred in two trial participants; one trial participant who had just been extubated and another trial participant who went into cardiac arrest for another reason than hypoxaemia.

The trial participants receiving the standard treatment and what is recommended in current trauma guidelines (liberal oxygen) are not put at any additional risk compared to patients not enrolled in the study. However, we suspect this standard treatment is not always beneficial. As outlined in the background section, we hypothesise that a liberal supplemental oxygen strategy may be harmful and should be avoided as soon as possible. Thus, the restrictive supplemental oxygen (intervention group) may be associated with fewer side effects, with no additional risk, as seen in other studies. Therefore, we believe that this study may be beneficial for the single trial participant.

Finally, there is no risk of delaying treatment due to enrolment, as the treating physician treats the trial participant as usual, until the randomisation result is available, and the allocation has begun.
Therefore, we think that the study will add no risk for the included trial participants.

Protocol changes

Protocol changes can only be decided by the steering committee. All trial documents, including protocol amendments are available on the public TRAUMOX2 website and communicated to relevant parties when found appropriate.

Timeline of study progress

Inclusion began December 7th, 2021 and is expected to be completed early 2024. Data analysis and manuscript drafting will commence autumn 2024. And thus, the submission of the primary paper is expected at the beginning of year 2025.

Data monitoring and safety committee

An independent data monitoring- and safety committee (DMSC) has been set up. The committee includes a statistician. The committee will meet when information on 30-day mortality has been collected in 355 (approximately 25% of the sample size estimation) and 710 (approximately 50% of the sample size estimation) trial participants. Prior to the meeting, a statistician will perform an interim analysis with blinded data provided by the sponsor and principal investigator. Criteria for premature termination will be decided by the steering committee. Furthermore, the sponsor

has the responsibility to report the overall number of SAEs yearly to the DMSC. Detailed information on the DMSC is available on the study website.

Publication Policy

The study results will be published in an appropriate international peer-reviewed scientific journal. Once the study results are published, it will be announced on the study website. The study is registered, and study results will be disclosed by the coordinating principal investigator in one or more public clinical study registry(ies), according to national/international use, including both positive, negative and inconclusive results. The registration will include a list of the investigational centres. The steering committee and the primary centre investigator (active) will be listed as co-authors in the publications. If the centre involves prehospital inclusion the prehospital centre investigator (active) will be co-author. Top-enrolling centres will be able to designate one additional co-author for every completely documented 100 trial participants. Blinded outcome assessors and the statistician doing the analyses can also qualify as co-authors. All authors must fulfil the criteria for authorship according to the ICMJE group. Each contributing centre can designate a reasonable number of active collaborators that participates in the study administration. These collaborators will be mentioned in the TRAUMOX2-study group and will be trackable via PubMed. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to make the dataset available in whole or part for secondary analyses and scientific publication. The steering committee will consider proposals for secondary analyses based on the scientific quality of the proposal. Proposals will need to be revised and approved by the steering committee prior to submission.

Archiving of Documents

The investigator will keep the subject's files and original data according to the local methods and facilities. The investigator will maintain the trial documents as specified in the ICH-GCP-Guideline for 10 years. The investigator/ institution will take measures to prevent accidental or premature destruction of these documents.

Patient and Public Involvement

Patients were not involved in the planning of this study. Trial participants will be given the opportunity to access the outcomes of the study once published.

Discussion

Oxygen has been used for centuries, but the evidence supporting its use remains sparse. The trauma population is particularly exposed to high concentrations of oxygen[1,3,4,10,32,33], although evidence for supplementary oxygen for the trauma population is extremely limited.[6,34] This is also evident in the newly updated guidelines on oxygen use in adults in the emergency setting published by the British Thoracic Society.[35] In trauma, they recommend initial management with high-concentration oxygen therapy and a target SpO_2 of 94–98% for both hypoxaemic patients and patients 'at risk of hypoxaemia'. This, however, is a Grade D recommendation.

As mentioned in the introduction, a recently published meta-analysis in the *Lancet* concluded that clinicians should aim for a target SpO_2 of 94–96% in acutely ill patients.[8] Their analysis compared liberal versus conservative oxygen strategies and found increased rates of mortality for patients with SpO_2 above 96% compared to 94–96%. Of note, the trial sequential analysis in the meta-analysis was driven primarily by a single large randomised trial,[36] preventing the authors from excluding a small beneficial effect of liberal oxygen therapy. Furthermore, only one study on trauma patients was included.

Nonetheless, there is an increasing concern regarding the detrimental effects of hyperoxaemia, and thus targeting normoxaemia becomes appealing. However, the impact of pursuing normoxaemia on the prevalence of hypoxic episodes is unknown. Normoxia thus suddenly represents the fragile middle ground between two states of which we know one to be harmful and fear the other is too. However, in TRAUMOX1 maintenance of normoxaemia post trauma appeared feasible and there were few episodes of hypoxaemia.[20] Thus, TRAUMOX1 forms the basis of the current trial, TRAUMOX2, that aims to provide high-level evidence on the implications of supplemental oxygen.

In TRAUMOX2 the intervention is an SpO_2 target in the restrictive group and an FiO_2 target in the liberal group. Given the sigmoid shape of the oxygen dissociation curve, however, the PaO_2 resulting from a given FiO_2 and SpO_2 can vary greatly. Nevertheless, a trial must be feasible, and in the acute phase post trauma, careful titration of the PaO_2 is not feasible. A large retrospective study on 864,340 trauma patients found that trauma patients with and SpO_2> 97% in the emergency department had a higher risk of in-hospital mortality if they received supplemental oxygen.[7] A large randomised study on patients with myocardial infarction showed that targeting an SpO_2 of 94% resulted in a decrease in myocardial injury and myocardial infarct size.[37] Another study has shown a dramatic increase in the occurrence of hyperoxaemia when SpO_2 was above 95%,[38] and for those reasons, we have chosen SpO_2 94% to be the target in the restrictive group. The SpO_2 is recorded once every hour during the intervention and aims to represent the median SpO_2 during that hour. If multiple measurements are available, e.g. in the ICU, the median is calculated. It could be argued that continuous measurements, e.g. an SpO_2 every minute, would be favourable. However, the trial aims to be pragmatic, and everyday care in the general ward does not allow for careful titration of the SpO_2 more than once an hour.

Furthermore, the FiO_2 target in the liberal group is based on a guideline where oxygen is recommended for all trauma patients.[1] However, the recommendation is without a specific therapeutic goal. In TRAUMOX1, however, some clinicians were concerned about the concentration and duration of oxygen in the liberal group. Therefore, the concentration may be diminished to 60% or 12 L O_2/min on a non-rebreather mask once the trial participant reaches the OR, ICU, post-anaesthesia care unit or ward if the saturation is at least 98%.

In a retrospective study of intubated trauma patients we found that the FiO_2 seemed to be high in the first hours after trauma followed by a steady decline until a stable plateau of approximately 30 - 40% after 10-12 hours was reached.[39] Furthermore, in a randomised trial, administration of 80% compared with 30% oxygen in the perioperative period (median time with intervention= 5.5 hours) was associated with significantly increased long-term mortality.[40] Therefore, the duration of the intervention altogether has been diminished from 24 hours to eight hours to ensure to represent only the most acute phase post trauma until careful oxygen titration becomes possible.

It should be acknowledged that oxygen delivered to the tissues is dependent on numerous factors which are not directly accounted for in this trial, such as cardiac output and haemoglobin levels. In addition, some patients may have

pulmonal dysfunction with impaired oxygenation, for instance after chest trauma. The data collected in our pragmatic study will not allow a detailed analysis of all these factors, but haemoglobin levels and the presence of chest trauma are registered. The impact of both could subsequently be explored.

In TRAUMOX1 the median time from trauma to arrival in the trauma bay was 51 [29-68] minutes. In larger, more geographically challenging countries, however, this time gap may be much larger, and therefore prehospital inclusion is aimed for whenever possible in TRAUMOX2 to diminish time in the acute phase without any allocated intervention begun.

The primary outcome of the trial is the incidence of pulmonary complications and/or death within 30 days (combined outcome). This is done to increase the event rate, but also because both outcomes are very important to the trauma patient: the majority of trauma patients are free from co-morbidities and independent prior to their trauma,[41,42] but still each year 5.8 million people die as a result of trauma.[43] Furthermore, the incidence of pneumonia in trauma patients has been reported to be as high as 26-44% leading to disability and prolonged hospital stay.[44,45] Furthermore, trauma constitutes a major economic burden, as trauma-related costs were estimated to $671 billion in the United States alone in 2013.[46] Understanding whether supplemental oxygen plays a role in the outcome for the trauma patient is thus of utmost importance.

Figure 1 – Timeline of patients randomised to either liberal or restrictive oxygen approach from trauma to end of follow-up

Figure 2 – Pneumonia and ARDS (Acute Respiratory Distress) definitions

Funding

TRAUMOX2 is initiated by a research group of medical doctors in "Department of Anaesthesia and Trauma Centre, Centre of Head and Orthopaedics, Rigshospitalet, Denmark ". The work presented in this article is supported by Novo Nordisk Foundation grant NNF20OC0063985. In addition, the study is supported by The Lundbeck Foundation through a personal grant to author JB. Drug expenses are covered by the participating centres' departmental budget. Drug expenses beyond the normal department budget is also be covered by the participating centres.

Authors contribution

JB: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TA: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

VS: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
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Final approval of the version to be published; AND
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JH: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SY: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MK: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MVV: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
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EVL: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
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Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Final approval of the version to be published; AND
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CFE: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DLI: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

LSR: S Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JS: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest: None

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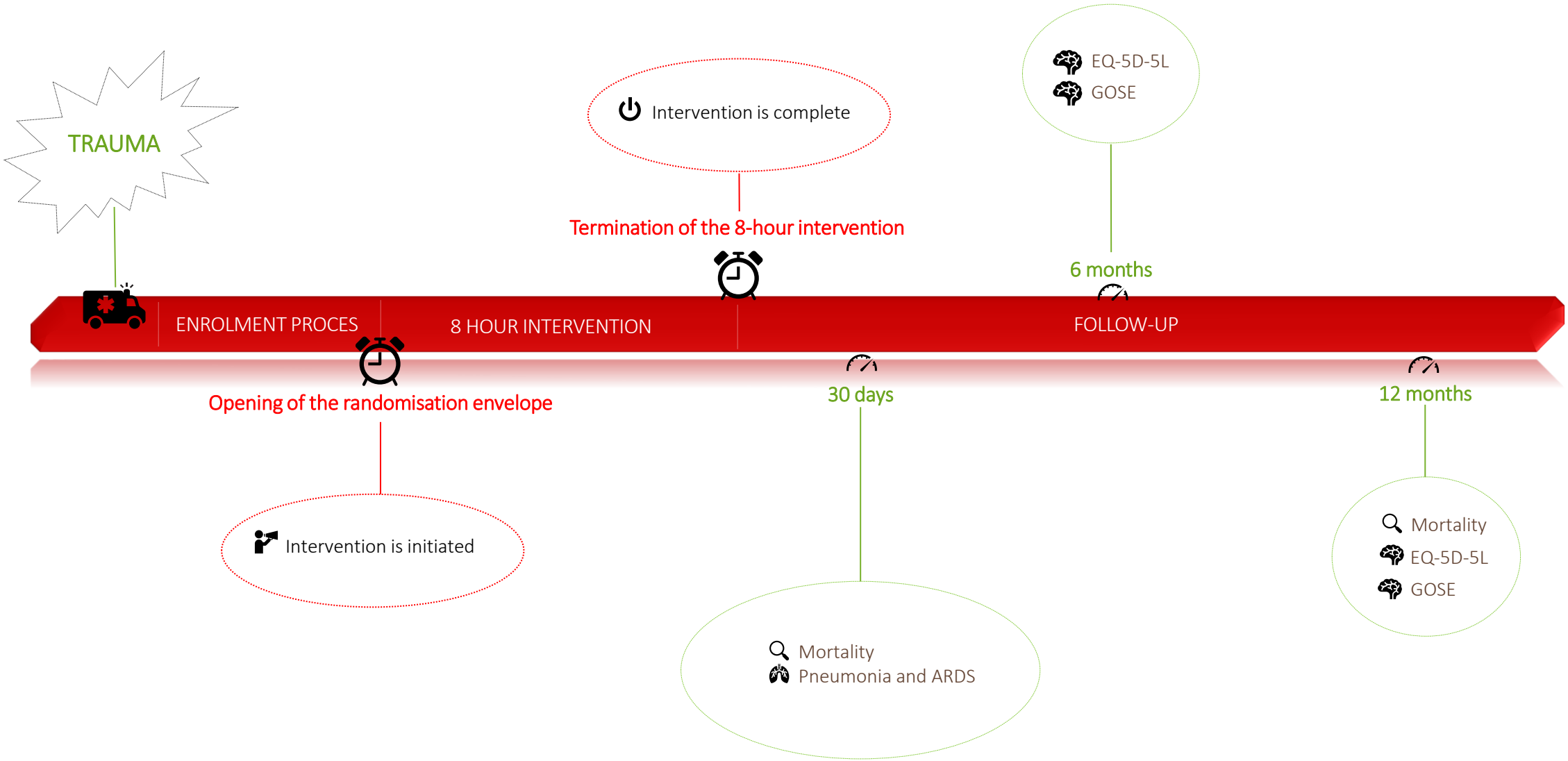
TRAUMA
ENROLMENT PROCES
8 HOUR INTERVENTION
FOLLOW-UP
Opening of the randomisation envelope
Intervention is initiated
Termination of the 8-hour intervention
Intervention is complete
30 days
Mortality
Pneumonia and ARDS
6 months
EQ-5D-5L
GOSE
12 months
Mortality
EQ-5D-5L
GOSE

Pneumonia	Two or more serial chest imaging test results with at least one of the following: - New and persistent OR progressive and persistent infiltrate/consolidation/cavitation Symptoms/laboratory: At least one of the following: - Temperature ≥ 38,5°C - Leukopenia (≤4000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3) - For adults >70 years old, altered mental status with no other recognized cause And at least two of the following: - New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements - New onset or worsening cough, or dyspnea, or tachypnea - Rales or bronchial breath sounds - Worsening gas exchange (e.g., O2 desaturations (e.g., PaO_2/FiO_2 <240 mmHg) increased oxygen requirements, or increased ventilator demand) Ventilator-associated pneumonia (VAP): A pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, AND the ventilator was in place on the date of event or the day before.
ARDS	Berlin definition: *Acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue…[with] hypoexemia and bilaterial radiographic opacities associated with increased venous admixture, increased physiological dead space and decreased lung compliance.* 1. *acute, meaning onset over 1 week or less* 2. *bilateral opacities consistent with pulmonary edema must be present and may be detected on CT or chest radiograph* 3. *Oxygenation difficulties are classified as mild, moderate or severe ARDS:* *mild: 200 mmHg < PaO2/FiO2 ≤ 300 mHg with PEEP/CPAP ≥ 5 cm H2O* *moderate: 100 mmHg < PaO2/FiO2 ≤ 200 mHg with PEEP ≥ 5 cm H2O* *severe: PaO2/FiO2 ≤ 100 mHg with PEEP ≥ 5 cm H2O*

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	✓ 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	✓ 2a	Trial identifier and registry name. If not yet registered, name of intended registry
	✓ 2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	✓ 3	Date and version identifier
Funding	✓ 4	Sources and types of financial, material, and other support
Roles and responsibilities	✓ 5a	Names, affiliations, and roles of protocol contributors
	✓ 5b	Name and contact information for the trial sponsor
	✓ 5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	✓ 5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	✓ 6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	✓ 6b	Explanation for choice of comparators
Objectives	✓ 7	Specific objectives or hypotheses
Trial design	✓ 8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	✓ 9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	✓ 10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	✓ 11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	✓ 11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	✓ 11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	✓ 11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	✓ 12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	✓ 13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	✓ 14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	✓ 15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	✓ 16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

	Allocation concealment mechanism	✓16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
	Implementation	✓16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)		✓ 17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
		✓ 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis			
Data collection methods		✓18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
		✓ 18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management		✓ 19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods		✓ 20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
		✓ 20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
		✓ 20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring			
Data monitoring		✓ 21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	✓	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	✓	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	✓	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	✓	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	✓	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	✓	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	✓	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	✓	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	✓	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	✓	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	✓	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	✓	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	✓	31b	Authorship eligibility guidelines and any intended use of professional writers
	✓	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	✓	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	✓	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparing Restrictive vs. Liberal Oxygen Strategies for Trauma Patients - The TRAUMOX2 Trial: Protocol for a Randomised Clinical Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064047.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2022
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	University of Copenhagen; University of Copenhagen, Institute of Clinical Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Adult anaesthesia < ANAESTHETICS, Adult intensive & critical care < ANAESTHETICS, TRAUMA MANAGEMENT, Respiratory physiology < THORACIC MEDICINE

Comparing Restrictive vs. Liberal Oxygen Strategies for Trauma Patients - The TRAUMOX2 Trial: Protocol for a Randomised Clinical Trial

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ABSTRACT

Introduction: Supplemental oxygen is commonly used in trauma patients, although it may lead to hyperoxaemia that has been associated with pulmonary complications and increased mortality. The primary objective of this trial, TRAUMOX2, is to compare a restrictive versus liberal oxygen strategy the first eight hours following trauma.

Methods and Analysis: TRAUMOX2 is an investigator-initiated, international, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial.
Adult patients with suspected major trauma are randomised to eight hours of a restrictive or liberal oxygen strategy. The restrictive group receives the lowest dosage of oxygen (≥21%) that ensures an SpO_2 of 94%. The liberal group receives 12-15 L O_2/min or FiO_2=0.6-1.0.
The primary outcome is a composite of 30-day mortality and/or development of major respiratory complications (pneumonia and/or ARDS).
With 710 participants in each arm we will be able to detect a 33% risk reduction with a restrictive oxygen strategy if the incidence of our primary outcome is 15% in the liberal group.

Ethics and dissemination: TRAUMOX2 is carried out in accordance with the Helsinki II Declaration. It has been approved by the Danish Committee on Health Research Ethics for the Capital Region (H-21018062) and The Danish Medicines Agency, as well as the Dutch Medical Research Ethics Committee Erasmus MS (NL79921.078.21 and MEC-2021-0932). A website (www.traumox2.org) is available for updates and study results will be published in an international peer-reviewed scientific journal.

Strengths and limitations

- TRAUMOX2 is an investigator-initiated, international, multicentre, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial.
- The oxygen treatment in current trauma management is challenged in this trial with trauma patients being randomised to two different oxygen strategies in the initial period post trauma.
- The intervention is open label, and the assessment of the primary outcome is blinded.
- The international setup will allow clinically relevant and generalizable results.
- Oxygen delivered to the tissues is dependent on other factors not directly accounted for in this trial, such as cardiac output and blood loss.

Registration details: European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) (2021-000556-19); www.clinicaltrials.gov. (NCT05146700)

INTRODUCTION

BACKGROUND AND RATIONALE

In trauma resuscitation supplemental oxygen is often administered to treat or prevent hypoxaemia as recommended by the Advanced Trauma Life Support manual.[1] This guideline does not have a specific therapeutic goal. Oxygen is administered in many other situations too, sometimes in a non-consistent manner[2–4] and very often without even being prescribed.[5] In a recent systematic review our group found the evidence for the use of supplemental oxygen in the trauma population to be sparse.[6] Nevertheless, in a large retrospective study on 864,340 trauma patients a propensity score matching analysis showed the administration of supplemental oxygen was associated with a significantly increased risk of in-hospital mortality and acute respiratory distress syndrome (ARDS).[7] Furthermore, a recent systematic review and meta-analysis comparing liberal versus restrictive oxygen strategy for a broad mix of acutely ill medical and surgical patients found an association between liberal oxygen administration and increased mortality.[8] Of note, only one small study on trauma patients (patients with traumatic brain injury), which did not report mortality data, was included. Conversely this study showed that degree of disability was significantly reduced at six months in the group receiving liberal compared to restrictive oxygen.[9]

Hyperoxaemia is a common finding in trauma patients[5,10] and in mechanically ventilated patients in general.[11,12] However, in the Intensive Care Unit (ICU) and in surgical patients hyperoxaemia has been associated with major pulmonary complications.[13,14] For example, a recent retrospective study found hyperoxaemia to be an independent risk factor for ventilator associated pneumonia .[14] Nevertheless, a highly debated recommendation from the World Health Organisation states that adult patients undergoing general anaesthesia for surgical procedures should receive an FiO_2 of 0.80 intraoperatively as well as in the immediate postoperative period for two to six hours to reduce the risk of surgical site infection.[15] A randomised study, however, found no difference in the risk of surgical site infection according to FiO_2 concentration intraoperatively.[16] Furthermore, a study on 152,000 mechanically ventilated patients found no association between hyperoxia and mortality during the first 24 hours in the ICU,[17] and another study on 14,000 mixed ICU patients found that a PaO_2 of approximately 18 kPa resulted in the lowest mortality.[18] Finally, a recent study randomised 2928 ICU patients to either low or high arterial oxygen tension target (defined as 8 vs 12 kPa), for a maximum of 90 days and found no difference in mortality.[19]

Therefore, whether the trauma population could benefit from a more restrictive supplemental oxygen approach than recommended by current international trauma guidelines presents a large and important knowledge gap. In a recent pilot randomised clinical trial (*TRAUMOX1*[20]*,* Clinicaltrials.gov Registration number: NCT03491644*)* we compared a restrictive and a liberal oxygen strategy for 24 hours after trauma (N=41) and found maintenance of normoxaemia following trauma using a restrictive oxygen strategy to be feasible. The study served as the basis for the following larger clinical trial; TRAUMOX2.

In TRAUMOX2 we hypothesize that a restrictive compared to a liberal oxygen strategy for eight hours following trauma will result in a lower rate of 30-day mortality and/or major respiratory complications (pneumonia and/or ARDS) (combined endpoint).

METHODS

Study setting

The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement and is version 1.6.[21] The SPIRIT 2013 checklist is presented in Appendix 1.

TRAUMOX2 is an investigator-initiated, international, multicentre, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial.

Participating trauma centres must be able to provide definitive treatment of trauma patients (tertiary care i.e. no transfer to more specialized institution needed), possess a trauma registry, and have an average of approximately 400 trauma patients per year. All trauma centres must be within the EU and thus the EU Clinical Trial Regulation are applied. A complete list of the study sites can be viewed on the trial website (www.traumox2.org).

Eligibility criteria

Patients aged 18 years or older, including fertile women, are included. Participants must have undergone blunt or penetrating trauma, be directly transferred from the scene of accident to one of the participating trauma centres and trigger trauma team activation (no secondary transfers from other hospitals). Moreover, the including physician must initially expect a hospital length of stay for 24 hours or longer. Patients with no/minor injuries after secondary survey are excluded if they are expected to be discharged within 24 hours to ensure only patients with a substantial trauma are included. Patients in cardiac arrest before or on admission and patients with a suspicion of carbon monoxide intoxication are excluded.

Interventions

Participants are randomised to eight hours of either restrictive or liberal supplemental oxygen treatment. The restrictive group receives the lowest dosage of oxygen (≥21%) that ensures an arterial oxyhaemoglobin saturation (SpO_2, measured by pulse oximetry) target of 94% either using no supplemental oxygen, a nasal cannula, a non-rebreather mask, or mechanical ventilation (intubated patients). Thus, only trial participants without a need for supplemental oxygen to maintain an SpO_2 ≥94% can saturate above 94%. The liberal group receives 15 L O_2/min via a non-rebreather mask for non-intubated trial participants and an FiO_2=1.0 for intubated trial patients in the prehospital setting, in the trauma bay and during intrahospital transportation. In the operating room, ICU, post-anaesthesia care unit and ward the flow/ FiO_2 may be reduced to 12 L O_2/min/FiO_2=0.6 if the arterial oxygen saturation ≥98%. In both groups, pre-oxygenation should be done prior to intubation.

Outcomes

The primary outcome is a composite of 30-day mortality and/or development of major respiratory complications (pneumonia and/or ARDS). Secondary outcomes include mortality at 30 days and 12 months post trauma, major respiratory complications (pneumonia and acute respiratory distress syndrome) within 30 days, hospital length of stay (HOS LOS), ICU length of stay (ICU LOS), days alive outside the ICU, time on mechanical ventilation (until 30 days), days alive without mechanical ventilation, re-intubation within 30 days, pneumonia post-discharge, surgical site infections within 30 days, episodes with hypoxaemia during intervention (SpO_2 <90%), and EQ-5D-5L score at six and 12 months post trauma, and Glasgow Outcome Scale-Extended (GOSE) at six and 12 months post trauma. The EQ-5D-5L score is a widely used generic measure for health-related quality of life, and [22] GOSE assesses physical and mental consequences of traumatic brain injury.[23]

Randomisation

Patients are randomised 1:1 in variable block sizes and stratified by centre (prehospital base or trauma centre) and tracheal intubation at inclusion. The randomisation table is generated outside of REDCap by a statistician otherwise not affiliated with the study. The allocation sequence list and block size are only known by the statistician and will remain concealed from the investigators. Prior to randomisation, a proxy consent must be obtained (or according to legislation in each country). Afterwards, randomisation is determined by opening a concealed envelope with information on allocation. The envelopes are available both pre- and in-hospital. Each concealed envelope contains a study ID that matches a study ID on the randomisation list generated by the statistician.

Participant timeline

Please see figure 1.

Blinding

The study outcome assessor- and analyst-blinded with regards to treatment: treating staff are aware of the trial participants' randomisation group. However, at least two allocation blinded primary outcome assessors (specialists in anaesthesia, intensive care, emergency medicine or similar) are appointed in each country to assess in-hospital lung complications (pneumonia and/or ARDS). Blinding is ensured by concealing all information indicative of the allocation prior to assessment.
The statistician and manuscript writers will be blinded towards the allocation of treatment once the trial ends when data is being analysed and the manuscript is drafted.

Recruitment and assignment of interventions

Depending on the possibilities of the recruiting site, patients are randomised and included either in the prehospital phase or in the trauma bay:

Prehospital phase (optional)

As soon as possible and after immediate and necessary life-saving procedures have been performed, a prehospital emergency physician (the including physician) assesses a patient eligible for inclusion. If all inclusion criteria are met, the including physician obtains proxy consent through a legally appointed study guardian (physician) by telephone. Proxy consent before inclusion may not be necessary in all participating countries. National rules and laws are followed in the specific country on both proxy consent as well as trial participant/trial participant's next-of-kin consent in general. Once the trauma patient is included, the including physician randomises the trial participant to the intervention (restrictive oxygen strategy) or control (liberal oxygen strategy) group by opening a concealed envelope with information on the allocation. The including physician registers the trial participant in an electronic database. If the trial participant is transported by helicopter, it is advised to fly at the lowest reasonable altitude to reduce the alterations from normal atmospheric oxygen tension at sea level. Treatment is initiated and continued for eight hours after enrolment. Time of initiation equals T0 (see figure 1).

Trauma bay

As soon as possible or after immediate and necessary life-saving procedures have been performed the including physician (e.g. the trauma leader or an attending anaesthesiologist) judges whether the patient is eligible for the study. If eligible, the including physician obtains proxy consent through a legally appointed study guardian (physician). Proxy consent before inclusion may not be necessary in all participating countries. National law is followed in the specific country on both proxy consent as well as trial participant/trial participant's next-of-kin consent in general. Once the trauma patient is included, the including physician randomises the trial participant to the intervention

(restrictive oxygen strategy) or control (liberal oxygen strategy) group by opening a concealed envelope with information on allocation. The including physician registers the trial participant in an electronic database. Treatment is initiated and continued for eight hours after enrolment. Time of initiation equals T0 (see figure 1) and must not be delayed more than 90 minutes after hospital arrival.

Consent

Consent procedures vary according to including location. In broad terms, the patients eligible for inclusion in the trial are temporarily incompetent because of the acute and severe condition related to their traumatic injuries. The trauma patients are eligible either on the scene of accident or upon arrival in the trauma bay where early resuscitation with the use of multiple interventions and even surgery may be necessary. Symptoms include severe pain, impaired consciousness, and early complications are circulatory and respiratory failure requiring emergency intubation. Some of these trial participants are expected to die. The intervention tested in this trial is pivotal to be given immediately in the early phase of resuscitation. In clinical trials aiming to improve treatment of traumatic injuries it is necessary to include unconscious and incompetent patients as no clinically relevant animal model exists. As soon as possible, local consent procedures are followed. In Denmark, proxy consent is first obtained through a legally appointed study guardian. Hereafter, consent is sought by the trial participants' next-of-kin as soon as-possible, and when possible, consent is sought by the trial participant. If the trial participant is not able to consent within 30 days, consent from the next-of kin is accepted as the final consent. If the next-of-kin is unavailable, a secondary proxy consent can be obtained through a legally appointed study guardian, and this can also be accepted as the final consent. Detailed consent procedures in specific locations can be found on the trial website.

Data collection methods, registration, and monitoring

Oxygen dosages and saturations are recorded every hour and two arterial blood gas analyses are obtained and noted in a paper data collection sheet specifically made for this study ("Randomisation, data collection sheet and REDCap inclusion", available on the study website). Further data collection is obtained by accessing the trial participants' medical records. Data points include trial participant characteristics (name, unique patient identifier, age, sex, height, weight), prehospital data (vital signs, trauma mechanism, details on supplemental oxygen in the prehospital phase (indication, SpO_2, supplemental oxygen yes/no, intubation yes/no, oxygen flow/FiO_2), Injury Severity Score, complete list of injuries, transportation mode to the trauma bay), time points (date and time of trauma, on-scene arrival and departure, trauma bay arrival, ICU/ward arrival, time of intubation/extubation/re-intubation for intubated trial participants, time of surgery, duration of surgery), hospital and ICU length of stay, vital signs on arrival to the trauma bay (including arterial blood gas analysis if available), in-hospital variables (pneumonia, ARDS, other infections (surgical site infection or sepsis)), ischaemic events within 7 days after admission (myocardial infarction or cerebral ischemia), Adverse Events and Serious Adverse Events (SAE), co-morbidities prior to trauma (categorised in heart disease, lung disease, other diseases), active smoker (yes/no), specifics of possible brain injury (type and extent) and other cerebral complications, and time until of death.

Trial participants with traumatic brain injury admitted to a neurosurgical intensive care unit can be monitored according to standard practice in the local facility. It is acceptable, but optional, to perform continuous intraparenchymal brain oxygen measurements.

For all TRAUMOX2 trial participants it is possible to deviate from the protocol if clinically justified by the treating physician. Such deviations should always be documented including the clinical justification.

Mortality status is collected through local registries or according to local practice. EQ-5D-5L and GOSE score are collected through telephone interviews, either with the trial participant or with the trial participant's next-of-kin or

caregiver. Possible pneumonia post-discharge is evaluated through medicines prescribed after hospital discharge in countries where this information is available.

All trial participants will have two arterial blood gasses (ABGs) drawn within the intervention period. The first ABG is drawn at hour 1 ± 30 minutes (T1) after randomisation (initiation of intervention is considered hour 0). If an ABG is not obtainable at hour 1 due to still being prehospital or other circumstances, the ABG must be obtained as soon as possible. The second ABG is drawn at hour 6 ± 2 hours (T6). If more than two ABGs are collected during the intervention (ABGs not related to the study), the ABGs closest to the specified time slots (T1 and T6) should be used for data entry.

Furthermore, the trial participant or his/her next-of-kin is asked for an additional and separate consent form, not directly related to this research project, to have their blood stored in a biobank established for future research. It is optional whether the participating centres contribute to the biobank.

Data is stored in an electronic, web-based, secure, centralised, user-friendly interface using a data collection sheet in REDCap[24] specifically made for this trial. This data management system is secure, fully compliant with all regulatory guidelines and a complete audit-trail for data entry validation. Trained members of the research team are responsible for data collection and entry into REDCap using local electronic clinical registries. Therefore, the electronic case report form (eCRF) is digital. In case of system malfunction, a paper version of the data collection sheet is available. The REDCap database is set up from Rigshospitalet in the Capital Region in Denmark and participating centres are invited to data entry in this database.

External monitoring of registered data is applied at all trial centres.

Definitions

Pneumonia is defined as per the CDC criteria[25].

ARDS is defined as per the Berlin definition[26].

Traumatic brain injury is defined as[27]:

- Severe: Abbreviated Injury Scale (AIS) ≥5
- Moderate: AIS 3–4
- Mild: AIS 1–2

Please see figure 2 for a detailed description of pneumonia and ARDS.

Statistical Analysis

In larger studies, mortality from trauma has been estimated to be around 6-12%,[28] and the incidence of ventilator associated pneumonia post trauma to be almost 30%.[14] With 710 trial participants in each arm, we will be able to detect a 33% risk reduction with a restrictive supplemental oxygen strategy (with 80% power at the 5% significance level) if the incidence of our primary outcome is 15% in the liberal group. Our primary analysis will be a modified intention-to-treat analysis, but a per-protocol analysis will also be carried out. A detailed statistical analysis plan, including the pre-specified subgroup analyses, will be made. In the primary analysis, we will exclude trial participants where no injuries are found, defined as Injury Severity Score=0.

If less than 5% of data required for any specific analysis on primary or secondary outcomes are missing, a complete case analysis will be performed. If more than 5% are missing, and it is concluded that data are not 'missing completely at random' inverse probability weighting will be used to correct possible bias.[29] A sensitivity analysis on the assumptions used for missing data will be done to verify robustness.

Inclusion of trial participants will end when the goal of 1420 evaluable trial participants has been reached including the 30-day follow up period. This means that the maximum number of trial participants will be 1600 as inclusion will continue during evaluation of the 30-day follow-up. EQ-5D-5L score and GOSE score at six months and 12 months will be obtained. Mortality at 30 days and 12 months will also be obtained. The primary composite outcome will be compared between the two groups using logistic regression reported as Odds Ratio with 95% CI. The primary analysis will be adjusted for age, sex, centre, intubated at randomisation (yes/no), and known pneumonia on admission (under treatment). Secondary outcomes will also be compared between the two groups using logistic regression for dichotomous data and linear regression for continuously valued outcomes. We will use a 5% significance level. Any changes or additional analyses will be reported.

In the per-protocol analysis, all trial participants with ≥1 major protocol violation will be removed.

Specified subgroup analyses will be made on trial participants initially intubated (within one hour of the accident) (yes/no), trial participants with ICU admission (yes/no), trial participants with moderate and severe traumatic brain injuries (yes/no), trial participants with chronic pulmonary disease (yes/no), registered episodes with hypoxaemia as well as an analysis on trial participants enrolled prehospital versus in-hospital. An analysis adjusted for Injury Severity Score will also be conducted.

The statistical analysis will be performed by a statistician.

Recruitment Status

August 19th, 2022 the trial had included 479 patients (34%) and recruitment is thus ongoing.

Adverse and serious adverse events

To monitor adverse events a TRAUMOX2 investigator assesses the trial participant's medical record once within the first 24 hours and every third day until discharge (maximum of 30 days).

This group of trial participants are expected to have a lot of complications. It is the established practice in trials on critically ill patients that adverse events are part of the natural trajectory of the primary disease process or expected complications of the critical illness.[30] Therefore, we have chosen to record only the occurrence of atelectasis and irritability of airway mucosa.

All SAEs are registered. The registration is done in REDCap and once a SAE registration is complete, the sponsor and coordinating investigator receives an e-mail notification immediately via the REDCap notification e-mail system.

Ethics and dissemination

Trial participant insurances are in place at all trial sites either through the national health insurance or through specifically supplied local trial insurances as required according to the specific trial sites and national regulations.

This RCT is carried out in accordance with the principles from the Helsinki II Declaration in its latest version.[31] The protocol has been approved by the Danish Committee on Health Research Ethics for the Capital Region of Denmark (H-21018062) and The Danish Medicines Agency, as well as the Dutch Medical Research Ethics Committee Erasmus MS (NL79921.078.21 and MEC-2021-0932). It is monitored by the regional Good Clinical Practice Unit. Data

management must be approved according to national legislation. Furthermore, the trial has been registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) (2021-000556-19) as well as on www.clinicaltrials.gov (NCT05146700).

Finally, a website (www.traumox2.org) is available for further information and updates on the trial.

Protocol changes

Protocol changes can only be decided by the steering committee. All trial documents, including protocol amendments are available on the public TRAUMOX2 website and communicated to relevant parties when found appropriate.

Timeline of study progress

Inclusion began December 7th, 2021 and is expected to be completed early 2024. Data analysis and manuscript drafting will commence autumn 2024. And thus, the submission of the primary paper is expected at the beginning of year 2025.

Data monitoring and safety committee

An independent data monitoring- and safety committee (DMSC) has been set up. The committee includes a statistician. The committee will meet when information on 30-day mortality has been collected in 355 (approximately 25% of the sample size estimation) and 710 (approximately 50% of the sample size estimation) trial participants. Prior to the meeting, a statistician will perform an interim analysis with blinded data provided by the sponsor and principal investigator. Criteria for premature termination will be decided by the steering committee. Furthermore, the sponsor has the responsibility to report the overall number of SAEs yearly to the DMSC. Detailed information on the DMSC is available on the study website.

Publication Policy

The study results will be published in an appropriate international peer-reviewed scientific journal. Once the study results are published, it will be announced on the study website. The study is registered, and study results will be disclosed by the coordinating principal investigator in one or more public clinical study registry(ies), according to national/international use, including both positive, negative and inconclusive results. The registration will include a list of the investigational centres. The steering committee and the primary centre investigator (active) will be listed as co-authors in the publications. If the centre involves prehospital inclusion the prehospital centre investigator (active) will be co-author. Top-enrolling centres will be able to designate one additional co-author for every completely documented 100 trial participants. Blinded outcome assessors and the statistician doing the analyses can also qualify as co-authors. All authors must fulfil the criteria for authorship according to the ICMJE group. Each contributing centre can designate a reasonable number of active collaborators that participates in the study administration. These collaborators will be mentioned in the TRAUMOX2-study group and will be trackable via PubMed. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to make the dataset available in whole or part for secondary analyses and scientific publication. The steering committee will consider proposals for secondary analyses based on the scientific quality of the proposal. Proposals will need to be revised and approved by the steering committee prior to submission.

Archiving of Documents

The investigator will keep the subject's files and original data according to the local methods and facilities. The investigator will maintain the trial documents as specified in the ICH-GCP-Guideline for 10 years. The investigator/ institution will take measures to prevent accidental or premature destruction of these documents.

Patient and Public Involvement

Patients were not involved in the planning of this study. Trial participants will be given the opportunity to access the outcomes of the study once published.

Discussion

Oxygen has been used for centuries, but the evidence supporting its use remains sparse. The trauma population is particularly exposed to high concentrations of oxygen[1,3,4,10,32,33], although evidence for supplementary oxygen for the trauma population is extremely limited.[6,34] This is also evident in the newly updated guidelines on oxygen use in adults in the emergency setting published by the British Thoracic Society.[35] In trauma, they recommend initial management with high-concentration oxygen therapy and a target SpO_2 of 94–98% for both hypoxaemic patients and patients 'at risk of hypoxaemia'. This, however, is a Grade D recommendation.

As mentioned in the introduction, a recently published meta-analysis in the *Lancet* concluded that clinicians should aim for a target SpO_2 of 94–96% in acutely ill patients.[8] Their analysis compared liberal versus conservative oxygen strategies and found increased rates of mortality for patients with SpO_2 above 96% compared to 94–96%. Of note, the trial sequential analysis in the meta-analysis was driven primarily by a single large randomised trial,[36] preventing the authors from excluding a small beneficial effect of liberal oxygen therapy. Furthermore, only one study on trauma patients was included.

Nonetheless, there is an increasing concern regarding the detrimental effects of hyperoxaemia, and thus targeting normoxaemia becomes appealing. However, the impact of pursuing normoxaemia on the prevalence of hypoxic episodes is unknown. Normoxia thus suddenly represents the fragile middle ground between two states of which we know one to be harmful and fear the other is too. However, in TRAUMOX1 maintenance of normoxaemia post trauma appeared feasible and there were few episodes of hypoxaemia.[20] Thus, TRAUMOX1 forms the basis of the current trial, TRAUMOX2, that aims to provide high-level evidence on the implications of supplemental oxygen.

In TRAUMOX2 the intervention is an SpO_2 target in the restrictive group and an FiO_2 target in the liberal group. Given the sigmoid shape of the oxygen dissociation curve, however, the PaO_2 resulting from a given FiO_2 and SpO_2 can vary greatly. Nevertheless, a trial must be feasible, and in the acute phase post trauma, careful titration of the PaO_2 is not feasible. A large retrospective study on 864,340 trauma patients found that trauma patients with and SpO_2> 97% in the emergency department had a higher risk of in-hospital mortality if they received supplemental oxygen.[7] A large randomised study on patients with myocardial infarction showed that targeting an SpO_2 of 94% resulted in a decrease in myocardial injury and myocardial infarct size.[37] Another study has shown a dramatic increase in the occurrence of hyperoxaemia when SpO_2 was above 95%,[38] and for those reasons, we have chosen SpO_2 94% to be the target in the restrictive group. The SpO_2 is recorded once every hour during the intervention and aims to represent the median SpO_2 during that hour. If multiple measurements are available, e.g. in the ICU, the median is calculated. It could be argued that continuous measurements, e.g. an SpO_2 every minute, would be favourable. However, the trial aims to be pragmatic, and everyday care in the general ward does not allow for careful titration of the SpO_2 more than once an hour.

Furthermore, the FiO_2 target in the liberal group is based on a guideline where oxygen is recommended for all trauma patients.[1] However, the recommendation is without a specific therapeutic goal. In TRAUMOX1, however, some clinicians were concerned about the concentration and duration of oxygen in the liberal group. Therefore, the concentration may be diminished to 0.60 or 12 L O_2/min on a non-rebreather mask once the trial participant reaches the OR, ICU, post-anaesthesia care unit or ward if the saturation is at least 98%.

In a retrospective study of intubated trauma patients we found that the FiO_2 seemed to be high in the first hours after trauma followed by a steady decline until a stable plateau of approximately 0.30-0.40 after 10-12 hours was reached.[39] Furthermore, in a randomised trial, administration of 0.80 compared with 0.30 oxygen in the perioperative period (median time with intervention= 5.5 hours) was associated with significantly increased long-term mortality.[40] Therefore, the duration of the intervention altogether has been diminished from 24 hours to eight hours to ensure to represent only the most acute phase post trauma until careful oxygen titration becomes possible.

It should be acknowledged that oxygen delivered to the tissues is dependent on numerous factors which are not directly accounted for in this trial, such as cardiac output and haemoglobin levels. In addition, some patients may have

pulmonal dysfunction with impaired oxygenation, for instance after chest trauma. The data collected in our pragmatic study will not allow a detailed analysis of all these factors, but haemoglobin levels and the presence of chest trauma are registered. The impact of both could subsequently be explored.

In TRAUMOX1 the median time from trauma to arrival in the trauma bay was 51 [29-68] minutes. In larger, more geographically challenging countries, however, this time gap may be much longer, and therefore prehospital inclusion is aimed for whenever possible in TRAUMOX2 to diminish time in the acute phase without any allocated intervention begun.

The primary outcome of the trial is the incidence of pulmonary complications and/or death within 30 days (combined outcome). This is done to increase the event rate, but also because both outcomes are very important to the trauma patient: the majority of trauma patients are free from co-morbidities and independent prior to their trauma,[41,42] but still each year 5.8 million people die as a result of trauma.[43] Furthermore, the incidence of pneumonia in trauma patients has been reported to be as high as 26-44% leading to disability and prolonged hospital stay.[44,45] Furthermore, trauma constitutes a major economic burden, as trauma-related costs were estimated to $671 billion in the United States alone in 2013.[46] Understanding whether supplemental oxygen plays a role in the outcome for the trauma patient is thus of utmost importance.

Figure 1 – Timeline of patients randomised to either liberal or restrictive oxygen approach from trauma to end of follow-up

Figure 2 – Pneumonia and ARDS (Acute Respiratory Distress) definitions

Funding

TRAUMOX2 is initiated by a research group of medical doctors in "Department of Anaesthesia and Trauma Centre, Centre of Head and Orthopaedics, Rigshospitalet, Denmark ". The work presented in this article is supported by Novo Nordisk Foundation grant NNF20OC0063985. In addition, the study is supported by The Lundbeck Foundation through a personal grant to author JB. Drug expenses are covered by the participating centres' departmental budget. Drug expenses beyond the normal department budget is also be covered by the participating centres.

Authors contribution

JB: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TA: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

VS: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
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Final approval of the version to be published; AND
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JH: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
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SY: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
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Final approval of the version to be published; AND
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MK: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MVV: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
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EVL: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
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Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Final approval of the version to be published; AND
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CFE: Substantial contributions to the conception, analysis and interpretation of data for the work; AND
Revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DLI: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

LSR: S Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JS: Substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work; AND
Drafting the work; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest: None

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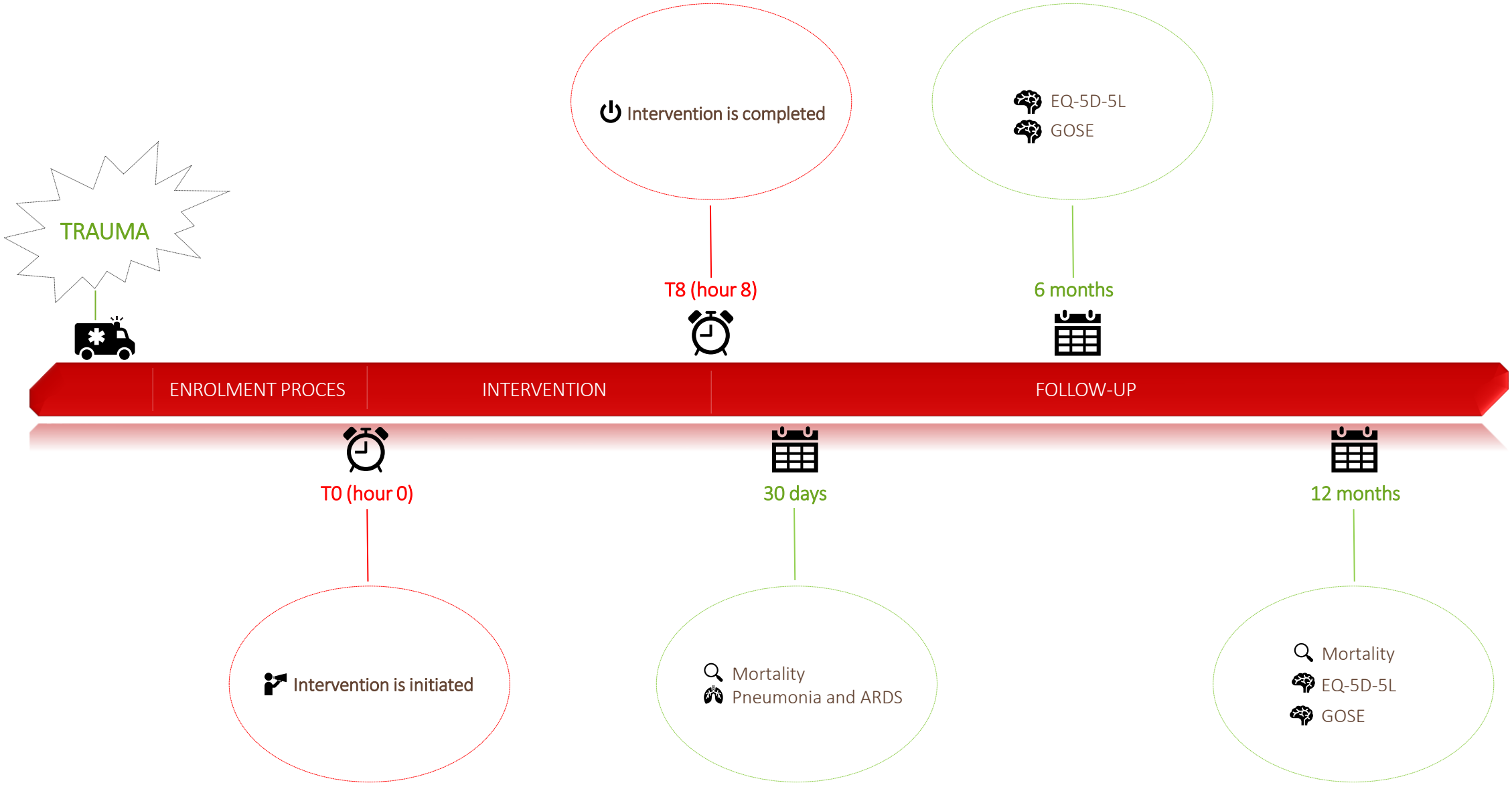
TRAUMA
ENROLMENT PROCES
INTERVENTION
FOLLOW-UP
T0 (hour 0)
T8 (hour 8)
30 days
6 months
12 months
Intervention is initiated
Intervention is completed
Mortality
Pneumonia and ARDS
EQ-5D-5L
GOSE
Mortality
EQ-5D-5L
GOSE

Pneumonia	Two or more serial chest imaging test results with at least one of the following: - New and persistent OR progressive and persistent infiltrate/consolidation/cavitation Symptoms/laboratory: At least one of the following: - Temperature ≥ 38,5°C - Leukopenia (≤4000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3) - For adults >70 years old, altered mental status with no other recognized cause And at least two of the following: - New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements - New onset or worsening cough, or dyspnea, or tachypnea - Rales or bronchial breath sounds - Worsening gas exchange (e.g., O2 desaturations (e.g., PaO_2/FiO_2 <240 mmHg) increased oxygen requirements, or increased ventilator demand) Ventilator-associated pneumonia (VAP): A pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, AND the ventilator was in place on the date of event or the day before.
ARDS	Berlin definition: *Acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue…[with] hypoexemia and bilaterial radiographic opacities associated with increased venous admixture, increased physiological dead space and decreased lung compliance.* 1. *acute, meaning onset over 1 week or less* 2. *bilateral opacities consistent with pulmonary edema must be present and may be detected on CT or chest radiograph* 3. *Oxygenation difficulties are classified as mild, moderate or severe ARDS:* *mild: 200 mmHg < PaO2/FiO2 ≤ 300 mHg with PEEP/CPAP ≥ 5 cm H2O* *moderate: 100 mmHg < PaO2/FiO2 ≤ 200 mHg with PEEP ≥ 5 cm H2O* *severe: PaO2/FiO2 ≤ 100 mHg with PEEP ≥ 5 cm H2O*

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	✓ 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	✓ 2a	Trial identifier and registry name. If not yet registered, name of intended registry
	✓ 2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	✓ 3	Date and version identifier
Funding	✓ 4	Sources and types of financial, material, and other support
Roles and responsibilities	✓ 5a	Names, affiliations, and roles of protocol contributors
	✓ 5b	Name and contact information for the trial sponsor
	✓ 5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	✓ 5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	✓ 6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	✓ 6b	Explanation for choice of comparators
Objectives	✓ 7	Specific objectives or hypotheses
Trial design	✓ 8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	✓ 9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	✓ 10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	✓ 11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	✓ 11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	✓ 11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	✓ 11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	✓ 12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	✓ 13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	✓ 14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	✓ 15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	✓ 16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

	Allocation concealment mechanism	✓ 16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
	Implementation	✓ 16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)		✓ 17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
		✓ 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis			
Data collection methods		✓ 18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
		✓ 18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management		✓ 19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods		✓ 20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
		✓ 20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
		✓ 20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring			
Data monitoring		✓ 21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	✓	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	✓	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	✓	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	✓	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	✓	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	✓	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	✓	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	✓	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	✓	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	✓	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	✓	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	✓	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	✓	31b	Authorship eligibility guidelines and any intended use of professional writers
	✓	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	✓	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	✓	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	✓ 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	✓ 2a	Trial identifier and registry name. If not yet registered, name of intended registry
	✓ 2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	✓ 3	Date and version identifier
Funding	✓ 4	Sources and types of financial, material, and other support
Roles and responsibilities	✓ 5a	Names, affiliations, and roles of protocol contributors
	✓ 5b	Name and contact information for the trial sponsor
	✓ 5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	✓ 5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	✓ 6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	✓ 6b	Explanation for choice of comparators
Objectives	✓ 7	Specific objectives or hypotheses
Trial design	✓ 8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Page number
1
4
appendix attached
6
16
1, 3 and 16
Page 5

Methods: Participants, interventions, and outcomes			
Study setting	✓	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	✓	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	✓	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	✓	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	✓	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	✓	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	✓	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	✓	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	✓	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	✓	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	✓	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

[6,7]	Allocation concealment mechanism	✓ 16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
[6,7]	Implementation	✓ 16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
[6,7]	Blinding (masking)	✓ 17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
[6,7]		✓ 17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
[6-9]	Data collection methods	✓ 18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
		✓ 18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
[6-9]	Data management	✓ 19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
[9,10]	Statistical methods	✓ 20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
		✓ 20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
		✓ 20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
[10, 11]	Data monitoring	✓ 21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	✓	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms [10, 11]	✓	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing [11, 12]	✓	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination [10, 11]			
Research ethics approval	✓	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments [11]	✓	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent [7]	✓	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	✓	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality [8]	✓	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests [16]	✓	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data [11]	✓	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care [NA]	✓	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy [12]	✓	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
[12]	✓	31b	Authorship eligibility guidelines and any intended use of professional writers
[NA]	✓	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

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WHO Trial Registration Data Set (Version 1.3.1)

The minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered. There are currently 24 items in the WHO Trial Registration Data Set. It is sometimes referred to as the TRDS.

1. **Primary Registry and Trial Identifying Number**
   Name of Primary Registry, and the unique ID number assigned by the Primary Registry to this trial.

   Page 4

2. **Date of Registration in Primary Registry**
   Date when trial was officially registered in the Primary Registry.

   December 7, 2021

3. **Secondary Identifying Numbers**
   Other identifiers besides the Trial Identifying Number allocated by the Primary Registry, if any. These include:
   - The Universal Trial Number (UTN)
   - Identifiers assigned by the sponsor (record Sponsor name and Sponsor-issued trial number (e.g. protocol number))
   - Other trial registration numbers issued by other Registries (both Primary and Partner Registries in the WHO Registry Network, and other registries)
   - Identifiers issued by funding bodies, collaborative research groups, regulatory authorities, ethics committees / institutional review boards, etc.

   Page 4

   All secondary identifiers will have 2 elements: an identifier for the issuing authority (e.g. NCT, ISRCTN, ACTRN) plus a number.

   There is no limit to the number of secondary identifiers that can be provided.

4. **Source(s) of Monetary or Material Support**
   Major source(s) of monetary or material support for the trial (e.g. funding agency, foundation, company, institution).

   Page 16

5. **Primary Sponsor**
The individual, organization, group or other legal entity which takes responsibility for initiating, managing and/or financing a study. The Primary Sponsor is responsible for ensuring that the trial is properly registered. The Primary Sponsor may or may not be the main funder.

Page 3

6. **Secondary Sponsor(s)**
Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship.

A secondary sponsor may have agreed to:
- take on all the responsibilities of sponsorship jointly with the primary sponsor; or
- form a group with the Primary Sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or act as the Primary Sponsor's legal representative in relation to some or all of the trial sites.

Page 3 and page 16

7. **Contact for Public Queries**
Email address, telephone number and postal address of the contact who will respond to general queries, including information about current recruitment status.

"Note: The information provided in here is functional and not personal, it is recommended to provide institutional and not personal information. By providing this information the registrant consents that the information provided can or may be published on a public website. Once provided the information cannot be redacted or anonymized as a result of new privacy legislation such as the European General Data Protection Regulation (GDPR)".

Page 2

8. **Contact for Scientific Queries**
There must be clearly assigned responsibility for scientific leadership to a named Principal Investigator. The PI may delegate responsibility for dealing with scientific enquiries to a scientific contact for the trial. This scientific contact will be listed in addition to the PI.

"Note: The information provided in here is functional and not personal, it is recommended to provide institutional and not personal information. By providing this information the registrant consents that the information provided can or may be published on a public website. Once provided the information cannot be redacted or anonymized as a result of new privacy legislation such as the European General Data Protection Regulation (GDPR)".

The contact for scientific queries must include:

- Name and title, email address, telephone number, postal address and affiliation of the Principal Investigator, and;
- Email address, telephone number, postal address and affiliation of the contact for scientific queries about the trial (if applicable). The details for the scientific contact may be generic (that is, there does not need to be a named individual): e.g. a generic email address for research team members qualified to answer scientific queries.

Page 2

9. **Public Title**
Title intended for the lay public in easily understood language.

Page 1

10. **Scientific Title**
Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available.

Page 2

11. **Countries of Recruitment**
The countries from which participants will be, are intended to be, or have been recruited at the time of registration.

Page 6

12. **Health Condition(s) or Problem(s) Studied**
Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error).

If the study is conducted in healthy human volunteers belonging to the target population of the intervention (e.g. preventive or screening interventions), enter the particular health condition(s) or problem(s) being prevented.

Page 4 and pages 6-12

13. **Intervention(s)**
For each arm of the trial record a brief intervention name plus an intervention description.

Intervention Name: For drugs use generic name; for other types of interventions provide a brief descriptive name.

- For investigational new drugs that do not yet have a generic name, a chemical name, company code or serial number may be used on a temporary basis. As soon as the generic name has been established, update the associated registered records accordingly.

- For non-drug intervention types, provide an intervention name with sufficient detail so that it can be distinguished from other similar interventions.

Intervention Description: Must be sufficiently detailed for it to be possible to distinguish between the arms of a study (e.g. comparison of different dosages of drug) and/or among similar interventions (e.g. comparison of multiple implantable cardiac defibrillators). For example, interventions involving drugs may include dosage form, dosage, frequency and duration.

If the intervention is one or more drugs then use the International Non-Proprietary Name for each drug if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable.

If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g. "low-fat diet, exercise").

For controlled trials, the identity of the control arm should be clear. The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g. placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc).

Page 4 and pages 6-12

14. **Key Inclusion and Exclusion Criteria**
Inclusion and exclusion criteria for participant selection, including age and sex. Other selection criteria may relate to clinical diagnosis and co-morbid conditions; exclusion criteria are often used to ensure patient safety.

If the study is conducted in healthy human volunteers not belonging to the target population (e.g. a preliminary safety study), enter "healthy human volunteer".

Page 4 and pages 6-12

15. **Study Type**
Study type consists of:
   - Type of study (interventional or observational)
   - Study design including:
     - Method of allocation (randomized/non-randomized)
     - Masking (is masking used and, if so, who is masked)
     - Assignment (single arm, parallel, crossover or factorial)
     - Purpose
   - Phase (if applicable)

For randomized trials: the allocation concealment mechanism and sequence generation will be documented.

Page 4 and pages 6-12

16. **Date of First Enrollment**
Anticipated or actual date of enrolment of the first participant.

Page 11

17. **Sample Size**
Sample Size consists of:
    - Number of participants that the trial plans to enrol in total.
    - Number of participants that the trial has enrolled.

Page 9

18. **Recruitment Status**
Recruitment status of this trial:
    - Pending: participants are not yet being recruited or enrolled at any site
    - Recruiting: participants are currently being recruited and enrolled
    - Suspended: there is a temporary halt in recruitment and enrolment
    - Complete: participants are no longer being recruited or enrolled
    - Other

Page 10

19. **Primary Outcome(s)**
Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention.

The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effects of the intervention(s). Most trials should have only one primary outcome.

For each primary outcome provide:
    - The name of the outcome (do not use abbreviations)
    - The metric or method of measurement used (be as specific as possible)
    - The timepoint(s) of primary interest

Example:
Outcome Name: Depression
Metric/method of measurement: Beck Depression Score
Timepoint: 18 weeks following end of treatment

Page 4 and pages 6-12

20. **Key Secondary Outcomes**
Secondary outcomes are outcomes which are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest.

As for primary outcomes, for each secondary outcome provide:
- The name of the outcome (do not use abbreviations)
- The metric or method of measurement used (be as specific as possible)
- The timepoint(s) of interest

Page 4 and pages 6-12

21. **Ethics Review**
The ethics review process information of the trial record in the primary register database. It consists of:
- Status (possible values: Not approved, Approved, Not Available)
- Date of approval
- Name and contact details of Ethics committee(s)

Page 10

22. **Completion date**
Date of study completion: The date on which the final data for a clinical study were collected (commonly referred to as, "last subject, last visit").

Unknown

23. **Summary Results**
It consists of:
- Date of posting of results summaries
- Date of the first journal publication of results
- URL hyperlink(s) related to results and publications
- Baseline Characteristics: Data collected at the beginning of a clinical study for all participants and for each arm or comparison group. These data include demographics, such as age and sex, and study-specific measures.
- Participant flow: Information to document the progress and numbers of research participants through each stage of a study in a flow diagram or tabular format.
- Adverse events: An unfavorable change in the health of a participant, including abnormal laboratory findings, and all serious adverse events and deaths that happen during a clinical study or within a certain time period after

the study has ended. This change may or may not be caused by the intervention being studied.
- Outcome measures: A table of data for each primary and secondary outcome measure and their respective measurement of precision (eg a 95% confidence interval) by arm (that is, initial assignment of participants to arms or groups) or comparison group (that is, analysis groups), including the result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any.
- URL link to protocol file(s) with version and date
- Brief summary

Awaiting

24. **IPD sharing statement**
Statement regarding the intended sharing of deidentified individual clinical trial participant-level data (IPD). Should indicate whether or not IPD will be shared, what IPD will be shared, when, by what mechanism, with whom and for what types of analyses. It consists of:
- Plan to share IPD (Yes, No)
- Plan description

Page 12