Protocol

Version 1.6

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

Date: 23/02/2022

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ClinicalTrials.gov number: NCT05146700
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General information

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

Short title: TRAUMOX2

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Study information: The trial will be carried out in accordance with the protocol and the applicable laws in this field. The trial is registered at clinicaltrials.gov and at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database.

Date and signature (sponsor):

Date and signature (primary investigator):

Abbreviations

ABG	Arterial Blood Gas
AE	Adverse Event
AIS	Abbreviated Injury Scale
ARDS	Acute Respiratory Distress Syndrome
DMSC	Data monitoring and safety committee
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FiO2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GOSE	Glasgow Outcome Scale Extended
HOS	Hospital
ICU	Intensive Care Unit
ISS	Injury Severity Score
LOS	Length Of Stay
OR	Operating Room
PACU	Post-Anaesthesia Care Unit
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

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Protocol synopsis

Item	Description
Study title	Comparing Restrictive vs. Liberal Oxygen Strategies for Trauma Patients: The TRAUMOX2 Trial
Study short name	TRAUMOX2
Protocol version	1.6
Study registration	EudraCT number: 2021-000556-19 ClinicalTrials.gov number: NCT05146700 Danish Research Ethics Committee number: H-21018062
Approvals	The Committee on Health Research Ethics for the Capital Region of Denmark (Regional Videnskabsetisk Komité), The Danish Medicines Agency (Lægemiddelstyrelsen) and The Knowledge Centre on Data Protection Compliance, Health Science and Innovation
Monitoring	The Good Clinical Practice Unit.
Funding	The trial is initiated by the sponsor and study investigators. It is funded by The Novo Nordisk Foundation and The Lundbeck Foundation. The drug expenses will be a part of the participating centres' normal budget.
Key words	Oxygen, trauma.
Background	In the trauma population, oxygen administration is often standard of care. However, the evidence supporting oxygen administration in this population is extremely limited. In a recent pilot study (TRAUMOX1), we found evidence that maintenance of normoxemia following trauma is feasible. Furthermore, we found that the incidence of mortality and lung complications tended to be higher amongst hyperoxemic patients.
Hypothesis	In TRAUMOX2, we hypothesize that a restrictive compared to a liberal oxygen strategy for the initial eight hours after trauma will result in a lower rate of 30-day mortality and/or major respiratory complications (pneumonia and ARDS) within 30 days (combined endpoint).
Study objective	The objective of this trial, TRAUMOX2, will be to compare the effect of a restrictive versus liberal oxygen strategy the first eight hours after trauma on the incidence of 30-day mortality and/or major respiratory complications (pneumonia and ARDS) within 30 days (combined endpoint).
Study design	An international, multicentre, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial with regards to

	treatment: treating staff will be aware of the randomisation group. While including patients for the study, the research team will also be aware of the randomisation allocation. The primary outcome assessors will be blinded by concealing all information indicative of the allocation of treatment. 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.
Inclusion criteria	- Age ≥18 years, including fertile women* - Blunt/penetrating trauma mechanism - Direct transfer from the scene of accident to one of the participating trauma centres - Trauma team activation - The enrolling physician must initially expect a hospital length of stay for 24 hours or longer **There is no added risk for enrolment of fertile women as oxygen administration is approved for this group of patients*
Exclusion criteria	- Patients in cardiac arrest before/at admission - Patients with a suspicion of carbon monoxide intoxication - Patients with no/minor injuries after secondary survey will be excluded if they are expected to be discharged <24 hours
Intervention	Centre specific: May start in the pre-hospital phase or in the trauma bay according to the possibilities at the participating centres. **8 hours of:** *INTERVENTION* Restrictive oxygen treatment: - Lowest oxygen delivery possible (≥21%) ensuring a saturation = 94% either using no supplemental oxygen, a nasal cannula, a non-rebreather mask or manual/mechanical ventilation (intubated trial participants) - Only trial participants receiving an FiO_2 = 0.21 can saturate >94% *CONTROL* Liberal oxygen treatment: - 15 L O_2/min flow for non-intubated trial participants in the pre-hospital phase, the trauma bay and during intrahospital transportation (in the OR, ICU, PACU and ward, the flow can be reduced to ≥12 L O_2/min if the arterial oxygen saturation is ≥98%) or - FiO_2 = 1.0 for intubated trial participants in the pre-hospital phase, the trauma bay and during intrahospital transportation (in the OR, ICU, PACU and ward, the FiO_2 can be reduced to ≥0.6 if the arterial oxygen saturation is ≥98%)

Evaluation criteria	Primary outcome: • Combined endpoint of 30-day mortality and/or major respiratory complications (pneumonia and ARDS) within 30 days Secondary outcomes: • Mortality at 30 days and 12 months after trauma • Major respiratory complications (pneumonia and ARDS) within 30 days • Hospital length of stay (HOS LOS), Intensive Care Unit length of stay (ICU LOS) and days alive outside the ICU • Time on mechanical ventilation (until 30 days), days alive without mechanical ventilation and number of re-intubations within 30 days • Pneumonia post-discharge within 30 days • Episodes of hypoxaemia during intervention (saturation <90%) • Surgical site infections within 30 days • EQ-5D-5L score at 6 months and 12 months post-trauma • GOSE score at 6 months and 12 months post-trauma
Number of trial participants	We wish to continue including up to 1600 trial participants. Once we have 710 trial participants in each arm with a 30-day follow up, yielding a total of 1420 trial participants, the trial will end.
Tracking of events	To monitor Adverse Events and Serious Adverse Events, a TRAUMOX2 investigator will assess the trial participant's medical record: - Once within the first 24 hours - Every third day until discharge (maximum of 30 days)
Risk benefit assessment	Restrictive oxygen: The risk of hypoxia is avoided as all trial participants are monitored closely during the eight hours intervention with continuous pulse-oximetry and arterial blood gases to avoid desaturations. Liberal oxygen: This treatment is similar to the current guidelines, and thus there will be no additional risk compared to trial participants not enrolled in the study.
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1. Background and rationale

In trauma resuscitation, supplemental oxygen is often administered both to treat and prevent hypoxemia as recommended both by the Advanced Trauma Life Support (ATLS) manual and the Pre-hospital Trauma Life Support (PHTLS) manual.[1,2] Oxygen is administered in many other situations too, sometimes in a non-consistent manner[3,4] and very often without even being prescribed.[5] In a recent systematic review our group found the evidence both for and against the use of supplemental oxygen in the trauma population to be extremely sparse.[6] However, 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.[7] 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.[8]

In mechanically ventilated patients hyperoxaemia is commonly observed (16-50%),[9,10] and hyperoxaemia is a common finding in trauma patients in general.[11] In addition to mortality, hyperoxaemia has been associated with major pulmonary complications in the Intensive Care Unit (ICU) as well as in surgical patients.[12,13] For example, a recent retrospective study found hyperoxaemia to be an independent risk factor for ventilator associated pneumonia (VAP).[13] Nevertheless, a highly debated recommendation from the World Health Organisation strongly recommends that adult patients undergoing general anaesthesia for surgical procedures 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.[14] Furthermore, a study on 152,000 mechanically ventilated patients found no association between hyperoxia and mortality during the first 24 hours in the ICU,[15] and another study on 14,000 mixed ICU patients found that a PaO_2 of approximately 18 kPa resulted in the lowest mortality.[16] Finally, a recent study randomised 2928 ICU patients to either low or high oxygenation (defined as 8 vs 12 kPa) for a maximum of 90 days and found no difference in mortality.[17] Therefore, whether the trauma population could benefit from a more restrictive supplemental oxygen approach than recommended by current international guidelines presents a large and important knowledge gap. In a recent pilot randomised clinical trial (*TRAUMOX1*[18], 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 normoxemia following trauma using a restrictive oxygen strategy to be feasible. The study served as the basis for the following larger clinical trial: TRAUMOX2.

Our experiences from TRAUMOX1 reflect the study design of the current trial proposal: TRAUMOX2. In TRAUMOX1 we experienced 24 hours to be slightly excessive to represent only the acute phase post trauma for which reason we will shorten this time-period to eight hours in TRAUMOX2. Furthermore, we found that several physicians had important concerns with the high dosage of oxygen in the liberal arm for which reason the concentration will be reduced. Finally, we did not randomise trauma patients in the pre-hospital phase, but instead on arrival at the trauma bay (median [IQR] time to randomisation: 7 [4-10] minutes, median [IQR] time from trauma to trauma bay arrival: 51 [29.0-67.5] minutes). To limit this inconsistent exposure to oxygen in the pre-hospital phase prior to inclusion we will initiate the intervention in the pre-hospital phase where possible in TRAUMOX2. This is consistent with our hypothesis that a liberal supplemental oxygen strategy may be detrimental and should be avoided as soon as possible. Hence, the study should be initiated in the prehospital setting in alignment with other time critical emergency research studies.

2. Study objectives

2.1 Primary objective

The objective of this trial, TRAUMOX2, will be to compare the effect of a restrictive versus liberal oxygen strategy the first eight hours following trauma on the incidence of 30-day mortality and/or major respiratory complications (pneumonia and ARDS) within 30 days (combined endpoint).

2.2 Hypothesis

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

2.3 Study registration

EudraCT number: 2021-000556-19
ClinicalTrials.gov number: NCT05146700
Danish Research Ethics Committee number: H-21018062

3. Methods

3.1 Study design and setting

The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.[19] We will conduct an international, multicentre, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled trial. Participating trauma centres must be able to provide definitive treatment of trauma victims (i.e. no transfer to more specialized institution needed), possess a trauma registry, and have a minimum average of approximately 400 trauma patients per year. All trauma centres must be within the EU and thus the EU Clinical Trial Regulation will be applied.

3.2 Inclusion criteria

- Patients aged ≥18 years, including fertile women*
- Blunt or penetrating trauma mechanism
- Direct transfer from the scene of accident to one of the participating trauma centres
- Trauma team activation
- The enrolling physician must initially expect a hospital length of stay for 24 hours or longer

**There is no added risk for enrolment of fertile women as oxygen administration is approved for this group of patients*

3.3 Exclusion criteria

- Patients in cardiac arrest before or on admission
- Patients with a suspicion of carbon monoxide intoxication
- Patients with no/minor injuries after secondary survey will be excluded if they are expected to be discharged <24 hours

3.4 Recruitment, consent and assignment of interventions

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

Pre-hospital phase (optional)

As soon as a pre-hospital emergency physician (the including physician) assesses a patient eligible for inclusion (meeting all inclusion criteria), the including physician obtains proxy consent through a legally appointed study guardian (physician) by telephone. In other countries than Denmark, proxy consent might not be mandatory before inclusion. National rules and laws will be 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. Allocation will be stratified based on the pre-hospital base, and whether the trial participant is intubated at inclusion. The envelope contains a specific study ID number matching the study ID number in the randomisation list. Futhermore, the envelope contains instructions on the allocated intervention regarding inclusion details. The including physician will register the trial participant in a database. In addition, the oxygen treatment and saturation registration form "Data collection sheet" will be part of the envelope in the paper "Randomisation, data collection sheet and REDCap inclusion". 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 the trauma team is activated, 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 will obtain proxy consent through a legally appointed study guardian (physician) i.e. by physical presence or by telephone if needed. In other countries than Denmark, proxy consent might not mandatory before inclusion. National rules and laws will be followed in the specific country on proxy consent and on trial participant/trial participant's next-of-kin consent in general. When the trauma patient is included, the including physician randomises the trial participant to the intervention (restrictive oxygen strategy) or control (liberal oxygen strategy) by opening a concealed envelope with information on allocation. Allocation will be based on trauma centre, and whether the trial participant is intubated at inclusion. The envelope contains a specific study ID number matching the study ID number in the randomisation list. Futhermore, the envelope contains instructions on the allocated intervention regarding inclusion details. The including physician will register the trial participant in a database. In addition, the oxygen treatment and saturation registration form "Data collection sheet" will be part of the envelope in the paper "Randomisation, data collection sheet and REDCap inclusion". 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.

3.4.1 Randomisation and blinding

Trial participants will be randomised 1:1 in variable block sizes and stratified by centre (pre-hospital base or trauma centre) and tracheal intubation at inclusion. The randomisation table will be generated outside of our electronic database REDCap (explained in section 3.7.2) by a biostatistician otherwise not connected to the study. The allocation sequence list and block sizes will only be known by the statistician and will remain

concealed from the investigators. Randomisation will be determined after proxy consent (or according to local legislation in each country) from opening a concealed envelope with information on allocation. The envelopes will be located both pre-hospital and in-hospital. Each concealed envelope will contain a study ID that matches a study ID in the randomisation list generated by the statistician.

The study will be an international, multicentre, parallel-grouped, superiority, outcome assessor- and analyst-blinded, randomised, controlled, clinical trial with regards to treatment: treating staff will be aware of the trial participants' randomisation group. While including trial participants for the study, the research team will be aware of the trial participants' oxygen allocation strategy. However, at least two allocation blinded primary outcome assessors (specialists in anaesthesia, intensive care, emergency medicine or similar) will be appointed at each centre to assess in-hospital lung complications (pneumonia and ARDS). Blinding will be 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.

3.4.2 Consent

The patients eligible for inclusion in the trial will be temporarily incompetent because of the acute and severe condition related to their traumatic injuries. The trauma patients will be 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 will 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. Therefore, we cannot delay enrolment and need to use the consent procedures for emergency research. To make clinical trials with the goal of improving the treatment of traumatic injuries it is necessary to include unconscious and incompetent patients as no clinically relevant animal model exists. As such, proxy consent will first be obtained through a legally appointed study guardian by telephone or by physical presence. In Denmark, national law dictates that you will need both a 1st proxy consent before inclusion and a 2nd proxy consent after inclusion and this will be followed in this study for inclusion of all trial participants. The legally appointed guardians have to be doctors (meeting the qualification level of an orthopaedic surgeon/intensivist on call at the specific centre or similar qualification level). It is up to each participating centre to decide who the legally appointed study guardians are and how the proxy consents are obtained. The legally appointed study guardians should always take care of the trial participant's interests when consenting to the study on behalf of the trial participant. Furthermore, they must be independent of the sponsor, investigators and the interests of this research project. Finally, they are not allowed to work in the same department as the investigator at the specific centre. The proxy consent form will be digital, and all signatures will be written on a smart phone or tablet using REDCap (a secure research electronic data capture system explained in details in the data management section). This electronic data system has dedicated functionalities for written consent and is considered completely safe for data management and storage. In other countries, centres must comply with specific legislation on this matter.

Hence, we consider all trauma patients to be without ability to consent to participation ("uden handleevne").

The study fulfills the following criteria from "komitéloven" in regard to research in acute situations:

§ 12:
"*Komiteen kan tillade, at et sundhedsvidenskabeligt forskningsprojekt, der angår kliniske forsøg med lægemidler, gennemføres uden indhentelse af samtykke efter §§ 3-5, hvis der i stedet indhentes stedfortrædende samtykke fra forsøgsværgen, og hvis forskningsprojektet efter sin karakter kun kan gennemføres i akutte situationer, hvor forsøgspersonen ikke er i stand til at afgive et informeret samtykke, og det ikke er muligt at indhente et stedfortrædende samtykke efter §§ 3 og 4.*

Stk. 2. Den forsøgsansvarlige skal snarest muligt efterfølgende søge at indhente informeret samtykke eller stedfortrædende samtykke efter §§ 3 og 4."

Hereafter, consent will be sought by the trial participants' next-of-kin as soon as-possible, and when possible, consent will be sought by the trial participant. If the trial participant is not able to consent within 30 days, consent from the next-of kin will be accepted as the final consent. In details, consent will be obtained in the following two steps:

1. Consent will be sought by the trial participant's next-of-kin as soon as possible (as early as possible after admission in an undisturbed environment) by the investigator. Efforts will be taken to ensure the conversation proceeds in an undisturbed room. Furthermore, at the initial conversation the next-of-kin will be informed about having the right to have a "bisidder" and have this relative next to the next-of-kin's side before the conversation proceeds if necessary. If it requires an additional waiting time, the investigator will respect this and return at a later point once the "bisidder" is present. ed. Additionally, the trial participant's next-of-kin will be informed of his/her right to take time to think of his/her choice ("betænkningstid"). This will be set at 24 hours. Until a decision has been reached, the trial participant will continue to be included.

2. Furthermore, the investigator will judge if the trial participant becomes capable of consenting himself/herself within the admission, and if this is the case, consent will be sought. Efforts will be taken to ensure the conversation proceeds in an undisturbed room. Furthermore, at the initial conversation the trial participant will be informed about having the right to have a "bisidder" and have this relative next to the trial participant's side before the conversation proceeds if necessary. If it requires an additional waiting time, the investigator will respect this and return at a later point once the "bisidder" is present. Additionally, the trial participant will be informed of his/her right to take time to think of his/her choice ("betænkningstid"). This will be set at 24 hours. Until a decision has been reached the trial participant will continue to be included. If the trial participant does not become capable of consenting himself/herself 30 days after the trauma, trial participant consent will no longer be sought.

Some trial participants are expected to remain in the state of being without the ability to consent to participation due to their injuries (continuated need of intubation) and for some of these trial participants, their next-of-kins are not possible to identify and contact. At day 30 after inclusion, no further attempts will be carried out to obtain informed consent. In these situations, the trial participant will be considered as continuing in the study for follow-up purposes on day 30, 6 months, and 12 months. Thus, the proxy consent from a legally appointed study guardian will be the consent on behalf of the trial participant.

All informed consent forms will be obtained by a member attached to the TRAUMOX2 research team consisting of either a medical doctor, nurse or medical student. The signed informed consent form from the trial participant/trial participant's next-of-kin will be available in the eletronic secure database, REDCap, in Denmark according to national legislation. In other countries than Denmark, national law will be followed regarding storage of the informed consent. It will be made clear, both verbally and in a written manner, that participation is voluntary and can be withdrawn at any time without affecting the treatment of the trial participant. It will also be made clear that the informed consent from the trial participant/trial participant's next-of-kin contains a permission for the personnel involved in the study, The Good Clinical Practice Unit (monitor of the study) and the Danish Medicines Agency (due to their legislative control inspection of the study) to gather information from the trial participant's medical record. According to the standard informed consent form from the National Ethics Committee regarding competent participants, the participant can choose to be informed about secondary findings due to their treatment at the hospital. As part of this trial, we do not do any diagnostic tests, and therefore, we find this question redundant since the responsibility of informing the patient about these eventual findings are on the treating physician.

3.5 Intervention and control group

Trial participants will be randomised to eight hours of either restrictive or liberal supplemental oxygen treatment.

3.5.1 Restrictive oxygen treatment (intervention group)

The restrictive group will receive the lowest dosage of oxygen (≥21%) ensuring an arterial oxyhemoglobin saturation (SpO_2) target = 94% either using no supplemental oxygen, a nasal cannula, a non-rebreather mask (non-intubated trial participants) or manual/mechanical ventilation (intubated trial participants). Pre-oxygenation should be done as usual prior to intubation. Only trial participants receiving an FiO_2 = 0.21 can saturate >94%.

3.5.2 Liberal oxygen treatment (control group)

The liberal group will for non-intubated trial participants receive 15 L O_2/min via a non-rebreather mask in the pre-hospital phase, the trauma bay and during intrahospital transportation (in the OR, ICU, PACU and ward, the flow can be reduced to ≥12 L O_2/min if the arterial oxygen saturation is ≥98%). The liberal group will for intubated trial participants receive an FiO_2 = 1.0 in the pre-hospital phase, the trauma bay and during intrahospital transportation (in the OR, ICU, PACU and ward, the FiO_2 can be reduced to FiO_2 ≥0.6 if the arterial oxygen saturation ≥98%).

3.5.3 Scheme overview of the intervention process

RANDOMISATION *Either in the prehospital setting or in the trauma bay*		
	Restrictive oxygen treatment *Intervention*	**Liberal oxygen treatment** *Control*

	Intubated trial participants *Positive end expiratory pressure (PEEP) at physician discretion*	**Non-intubated trial participants***	**Intubated trial participants** *Positive end expiratory pressure (PEEP) at physician discretion*	**Non-intubated trial participants***
Prehospital setting or trauma bay	Connected to ventilator FiO_2: Lowest value ensuring a saturation = 94% Only trial participants receiving an FiO_2 = 0.21 (or lowest possible) can saturate >94% Pre-oxygenation as usual prior to intubation	No supplemental oxygen/nasal cannula/non-rebreather mask depending on the saturation If saturation is <94%: Lowest O_2 flow (between 0-15 L/min) ensuring a saturation = 94% Only trial participants receiving no supplemental oxygen can saturate >94%	Connected to ventilator FiO_2 = 1.0	A non-rebreather mask O_2 flow = 15 L/min
Intrahospital transportation (trauma center to OR, ICU, PACU or ward)	Connected to transportable ventilator FiO_2: Lowest value ensuring a saturation = 94% Only trial participants receiving an FiO_2 = 0.21 can saturate >94% Pre-oxygenation as usual prior to intubation	No supplemental oxygen/nasal cannula/non-rebreather mask depending on the saturation If saturation is <94%: Lowest O_2 flow (between 0-15 L/min) ensuring a saturation = 94% Only trial participants receiving no supplemental oxygen can saturate >94%	Connected to transportable ventilator FiO_2 = 1.0	A non-rebreather mask O_2 flow = 15 L/min
Operating room	Connected to ventilator	Pre-oxygenation as usual prior to intubation	Connected to ventilator	Pre-oxygenation as usual prior to intubation

	FiO_2: Lowest value ensuring a saturation = 94% Only trial participants receiving an FiO_2 = 0.21 can saturate >94% Pre-oxygenation as usual prior to intubation	After intubation: Ventilator FiO_2: Lowest value ensuring a saturation = 94% Only trial participants receiving an FiO_2 = 0.21 can saturate >94%	FiO_2 can be reduced to ≥0.6 if the arterial oxygen saturation is ≥98%	After intubation: Ventilator FiO_2 can be reduced to ≥0.6 if the arterial oxygen saturation is ≥98%
ICU or PACU or ward	Connected to ventilator FiO_2: Lowest value ensuring a saturation = 94% Only trial participants receiving an FiO_2 = 0.21 can saturate >94% Pre-oxygenation as usual prior to intubation	No supplemental oxygen/nasal cannula/non-rebreather mask depending on the saturation If saturation is <94%: Lowest O_2 flow (between 0-15 L/min) ensuring a saturation = 94% Only trial participants receiving no supplemental oxygen can saturate >94%	Connected to ventilator FiO_2 can be reduced to ≥0.6 if the arterial oxygen saturation is ≥98%	A non-rebreather mask O_2 flow can be reduced to ≥12 L/min if the arterial oxygen saturation is ≥98%

The duration of the intervention is eight hours.

All trial participants will have two arterial blood gasses (ABGs) drawn within the intervention period in order to adjust supplemental oxygen treatment according to allocation.

The 1st ABG will be drawn at **hour 1 ± 30 minutes (T1)** after randomisation (initiation of intervention is considered hour 0). If an ABG is not obtainable at T1 due to still being pre-hospital or other circumstances, the ABG must be obtained as soon as possible.

The 2nd ABG will be drawn at **hour 6 ± 2 hours (T6)** after randomisation.

**In case non-intubated trial participants require intubation, this is done and the study is continued for intubated trial participants in the same arm.*

3.5.4 Tracking of oxygen

Oxygen administration and saturation for ventilated trial participants is automatically tracked through the ventilator and transferred to the electronic medical record. The caregiver will note it in a document made specificailly for this study ("Randomisation, data collection sheet and REDCap inclusion", appendix 9).

For non-ventilated trial participants, caregivers will track oxygen dosages and saturations every hour and note it in a document made specificailly for this study ("Randomisation, data collection sheet and REDCap inclusion", appendix 9).

3.5.5 Other treatment

All other drugs administered to the enrolled trial participant will be given as per usual.

3.5.6 Withdrawal from the study

In accordance with the Helsinki Declaration, trial participant's/trial participant's next-of-kin consent can be withdrawn at any time, for any reason. Likewise, the investigator can also withdraw trial participants from the trial at any time. The reason for withdrawal will be noted in the electronic Case Report Form.

3.5.7 Participant timeline

Please see figure 1.

3.6 Outcomes

3.6.1 Primary outcome

The primary outcome will be the incidence of 30-day mortality and/or major respiratory complications (pneumonia and ARDS) within 30 days (combined endpoint).

3.6.2 Secondary outcomes

The secondary outcomes will include:

- Mortality at 30 days and 12 months after trauma
- Major respiratory complications (pneumonia and ARDS) within 30 days
- HOS LOS, ICU LOS and days alive outside the ICU
- Time on mechanical ventilation (until 30 days), days alive without mechanical ventilation and number of re-intubations within 30 days
- Pneumonia post-discharge within 30 days
- Episodes of hypoxaemia during intervention (saturation <90%)
- Surgical site infections within 30 days
- EQ-5D-5L score at 6 and 12 months post-trauma
- GOSE score at 6 months and 12 months post-trauma

3.7 Data collection methods, registration and monitoring

Oxygen dosages and saturations will be recorded every hour and noted in a paper data collection sheet specifically made for this study ("Randomisation, data collection sheet and REDCap inclusion", appendix 9).

Further data collection will be obtained by accessing the trial participants' medical records. Data points will include:

- Patient characteristics: Name, unique patient identifier (Danish Central Personal Register Number ("CPR nummer"), age, sex, height, weight
- Pre-hospital circumstances: Vital signs, trauma mechanism, details on supplemental oxygen in the pre-hospital phase (indication, SpO_2, supplemental oxygen yes/no, intubation yes/no, oxygen flow/FiO_2), Injury Severity Score (ISS), 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 (myocardial infarction or cerebral ischemia)
- Adverse Events (AE) 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 such as cerebral ischemia
- Date 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. Brain oxygen measurements are influenced by placement of the catheter and often less reliable in the first hours of measurement, hence only a factor in a fraction of the eight-hour intervention period in TRAUMOX2.

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 in REDCap.

Mortality status will be collected through registries if possible or according to local practice. EQ-5D-5L score and GOSE score will be collected through telephone interviews, either with the trial participant or with the trial participants next-of-kin or caregiver. Possible pneumonia post-discharge will be 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 during the intervention. The 1st ABG will be 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 pre-hospital or other circumstances, the ABG must be obtained as soon as possible. The 2nd ABG will be 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 the specified time slots (T1 and T6) should be used for data entry.

3.7.1 Establishment of a biobank for future research

When consent is obtained from a trial participant or from a trial participant's next-of-kin to participate in TRAUMOX2, we will also ask in an additional and separate consent form, not directly related to this research project, if the trial participant wishes to participate in a biobank containing their blood established for future research. The data authorities in Denmark will be applied for storage and the informed consent from the trial participant/trial participant's next-of-kin will be digital in REDCap. It is optional whether the participating centres contribute to the biobank. The management of this biobank will follow the laws of GDPR (in Danish it is called "databeskyttelsesforordningen og databeskyttelsesloven") until a specific research question is established and a research protocol is made. Thus, an application for the permission of a specific research project will be handed in to the "Regionale Videnskabsetisk Komité". In this way, a permission will be seeked to do research on the biobank material without obtaining consent from the trial participants again.

3.7.2 Data management

All the above data will be stored in an electronic, web-based, secure, centralised, user-friendly interface using a data collection sheet in REDCap[20] specifically made for this trial. This data mangement system is secure, fully compliant with all regulatory guidelines and a complete audit-trail for data entry validation. Trained members of the research team will be responsible for data collection and entry into REDCap using local electronic clinical registries. Therefore, the electronic case report form (eCRF) will be digital. In case of system malfunction, a paper version of the data collection sheet ("Randomisation, data collection sheet and REDcap inclusion", appendix 9) will be available. The REDCap database will be set up from Rigshospitalet in the the Capital Region and participating centres will be invited to data entry in this database.

External monitoring of registered data will be applied at all trial centres following a monitoring plan developed in collaboration with the good clinical practice (GCP) unit at Copenhagen University Hospital according to GCP standards. Furthermore, the laws on "General Data Protection Regulation" (GDPR; in Danish: "databeskyttelsesforordningen og databeskyttelsesloven") will be followed. The data management will be also be registered internally at Region Hovedstadens own data management center The Knowledge Centre on Data Protection Compliance, Health Science and Innovation. The investigators of the trial will handle all information confidentially (tavshedspligt).

3.7.3 Data definitions

Pneumonia will be defined as per the CDC criteria.[21]
ARDS will be defined as per the Berlin definition.[22]
Traumatic brain injury will be defined as[23]:

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

3.8 Statistical analysis

In TRAUMOX1, the primary combined endpoint occurred in 20% in the restrictive group and 33% in the liberal group. In larger studies, mortality from trauma has been estimated to be around 6-12%[24], and the incidence for ventilator associated pneumonia post trauma to be almost 30%[13]. 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 ISS = 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' (MCAR criterion),[25] inverse probability weighting will be used to correct this bias. 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 6 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 (OR) 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 Fisher's exact test/Chi^2 test for categorical data and competing risk survival analyses for continuous data. 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. Please see section 3.8.1 for definitions of major protocol violations.

Pre-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 obstructive pulmonary disease (yes/no), 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 biostatistician.

3.8.1 Major protocol violations

A major protocol violation will be defined as:

- Restrictive O_2 group: during the intervention period

  - For non-intubated trial participants: Supplemental oxygen ≥3 L O2/min and having an SpO2 ≥98% recorded in two consecutive hourly values in the data collection sheet: "Randomisation, data collection sheet and REDCap inclusion"

  - For intubated trial participants: FiO2 ≥0.4 and having an SpO2 ≥98% recorded in two consecutive hourly values in the data collection sheet: "Randomisation, data collection sheet and REDCap inclusion"

- Liberal O_2 group: during the intervention period

  - For non-intubated trial participants: Supplemental oxygen <3 L O2/min in two consecutive hourly values in the data collection sheet: “Randomisation, data collection sheet and REDCap inclusion”

  - For intubated trial participants: FiO2 <0.4 in two consecutive hourly values in the data collection sheet: “Randomisation, data collection sheet and REDCap inclusion”

4. Drug management and accounting

4.1 Drug management

The investigated drug will be handled by the usual providers: Air Liquide A/S, Strandmøllen A/S and Linde Gas A/S.

4.2 Drug accounting

As the consumption of the trial medicine, oxygen, is continuous in all prehospital and intrahospital units, the providers (Strandmøllen A/S, Linde Gas A/S and Air Liquide A/S) will register batch numbers and expiration dates as usual. Detailed accounting and registration of the drugs will not be possible, as oxygen runs through central pipelines and thus cannot be tracked on an individual trial participant level. However, we foresee no possible complications or risks beyond the existing, which will be entirely unrelated to this study. Any potential problems with the delivery will not affect the enrolled trial participants any further than it would were they not enrolled in the study. No other methods to study oxygen at our institution are possible. Therefore, appendix 12 (“Produktresuméer for oxygen ved Air Liquide, Strandmøllen og Linde Gas, kryogen og komprimeret”) will be the most detailed available source of drug accounting and thus serve as the primary source.

5. Safety management

5.1 Definitions

The following definitions will be used[26]:

- Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product is adminsitered and which does not necessarily have a causal relationship with this treatment.

- Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

- Suspected Unexpected Serious Adverse Reaction (SUSAR): A suspected, serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

5.2 Tracking of events

The local investigators at each centre is responsible for recording the different types of AEs and SAEs in the trial participant's Case Report Form in REDCap. The specific investigator will assess the correlation between an event and trial medicine using the following AE/SAE event policy:

- 1: Unrelated – No temporal context; other etiologies are more likely to be the cause
- 2: Possible related – Less clear connection; other etiologies are also possible
- 3: Probably related – Clear temporal correlation with medication discontinuation, and not reasonably explained by the known clinical condition of the subject
- 4: Related – Clear temporal relationship with rehabilitation test or clinical assessment

To monitor AEs and SAEs, a TRAUMOX2 investigator will assess the trial participant's medical record:

- Once within the first 24 hours
- Every third day until discharge (maximum of 30 days)

5.3 Adverse Events and Serious Adverse Events

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.[27]

Therefore, we have chosen to record only the following AEs:

- Atelectasis
- Irritability of airway mucosa

We will register all SAEs. The registration will be done in REDCap and once a SAE registration is complete, the sponsor and coordinating investigator will receive an e-mail notification within 24 hours via the REDCap notification e-mail system. Thus, the law on immediate notifying (within 24 hours after it has come to an investigator's knowledge) the sponsor about SAEs is being followed.

5.4 Suspected Unexpected Serious Adverse Reactions

All potential SUSARs will be reported to the sponsor within 24 hours of discovery. If the sponsor believes that a trial participant has a SUSAR which results in death or is in a life-threatening condition, it will be reported as soon as possible to the Danish Medicines Agency and The Committee on Health Research Ethics and no later than 7 days after it has come to sponsor's knowledge. No later than 8 days after the report (15 days in total), sponsor must inform the mentioned authorities about all relevant information on the follow-up of the SUSAR. All other trial participants that have a SUSAR that do not result in death or in life-threatening conditions must be reported no later than 15 days after sponsor has been made aware of these.

5.5 Reporting

Once a year, a report with all SUSARs will be sent to The Danish Medicines Agency and The Committee on Health Research Ethics.

After the last trial participant, last visit (1420 trial participants with a complete 30-day, 6- and 12-month follow-up), the end of the trial will be reported within 90 days to the relevant authorities or according to national law. All events, reactions and results of the study will be reported to the EudraCT database results within a year after termination of the study.

6. Study administration

6.1 Ethics and dissemination

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

This RCT will be conducted in compliance with the published trial protocol, the Helsinki Declaration in its latest version,[28] the Good Clinical Practice (GCP) guidelines[29] and national laws in the participating countries. The protocol will be sent to the Danish Committee on Health Research Ethics for the Capital Region of Denmark and The Danish Medicines Agency. It will be monitored by the regional Good Clinical Practice Unit. Data management must be approved according to national legislation. We have written the protocol in accordance with the SPIRIT 2013 Statement[19] and will register the trial in the www.clinicaltrials.gov and European Union Drug Regulating Authorities Clinical Trials (EudraCT) registries before the enrolment of the first trial participant. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible.

As stated in section 3.4.2 regarding consent procedures in Denmark, the trial participants in this study are considered temporarily incompetent because of the acute and severe condition related to their traumatic injuries. Symptoms will 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. Current practice is that supplemental oxygen is administered as soon as possible after trauma often prehospitally. Thus, the intervention tested in this trial is pivotal to be given immediately in the early phase after trauma. Furthermore, it is stated above that a liberal supplemental oxygen strategy may be detrimental and should be avoided as soon as possible. Therefore, we cannot delay enrolment and need to use the consent procedures for emergency research. To make clinical trials with the goal of improving the treatment of traumatic injuries it is necessary to include unconscious and incompetent patients as no clinically relevant animal model exists. In other countries, national law will be followed in terms of including patients considered temporarily incompetent.

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 will be monitored with continuous pulse oximetry 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 only 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 hypoxemia.

The trial participants receiving the standard treatment and what is recommended in current guidelines (liberal oxygen) will not be put at any additional risk compared to trial participants 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 detrimental 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 trial participant populations. Therefore, we believe that this study may be beneficial for the single trial participant.
Finally, there will be no risk of delaying treatment due to enrolment, as the treating physician will be treating the trial participant as usual, until the randomisation results are available, and the allocation has begun. Therefore, we think that the study will add no risk for the included trial participants.

6.2 Timeline of study progress

Approvals will be applied for spring 2021 initially in Denmark. First inclusion is expected autumn 2021, enrolment completed spring 2023 and data analysis and manuscript drafting autumn 2023. The submission of primary paper is expected at the beginning of year 2024. See figure 2.

6.3 Publication publicy

The study results will be published in an appropriate international peer-reviewed scientific journals. When study results are published, it will be announced on the study website https://www.traumox2.org/. The study will be 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. 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 on the basis of the scientific quality of the proposal. Proposals will need to be revised and approved by the steering committee prior to submission.

6.4 Data monitoring and safety committee (DMSC)

An independent data monitoring- and safety committee (DMSC) will be set up. The committee will include a statistician. The committee will meet when 30-day follow-up of 355 (approximately 25% of the sample size estimation) and 710 (approximately 50% of the sample size estimation) trial participants has been obtained. Prior to the meeting, a biostatistician will perform an interim analysis with blinded data provided by the sponsor and principal investigator. Criteria for premature termination will be decided by steering committee. Furthermore, the sponsor has the responsibility to report the overall number of serious adverse events (SAEs) yearly to the DMSC. The DMSC charter has been approved by DMSC members and the Danish Medicines Agency. The content of the charter is:

Charter for the Data Monitoring and Safety Committee (DMSC) for TRAUMOX2

Version 1.0

Date: 21-12-2021

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

EudraCT number: 2021-000556-19
Danish Research Ethics Committee number: H-21018062
ClinicalTrials.gov number: NCT05146700

Chief investigator and sponsor: Professor Jacob Steinmetz, M.D., Ph.D.

Introduction

This charter will define the responsibilities of the independent DMSC, the members, the purpose of the DMSC and the timing of the meetings. The DMSC is answerable for the safety of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC is obliged to follow the EU Clinical Trials Directive 2001/20/EC while assessing the study and to keep all patient-level data confidential. The DMSC consists of three clinicians with expertise in critical emergency care research and an independent biostatistician. The DMSC members have been chosen in order to avoid any financial or intellectual conflicts of interest. The members have agreed to this task for the entire duration of the clinical trial. However, should any members leave the DMSC during the trial, the steering committee will appoint the replacement(s). The DMSC is independent from the sponsor and the trial investigators. The DMSC will be notified of all changes to the protocol or changes in trial conduct. The clinicians of the DMSC will be unpaid. The biostatistician will be paid for the hours spent on data analysis prior to the DMSC meetings.

Timing of the meetings

Two interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct (e.g. enrollment progression). The four members of the DMSC will meet either physically or online when 30-day follow-up data (primary outcome) of 355 (approximately 25 % of sample size estimation) and 710 (approximately 50 % of sample size estimation) patients have been obtained. The trial will continue while the DMSC review the data. The DMSC will be specifically notified by e-mail by the sponsor or coordinating investigator when approximately 20 % and 45 % of the patients are included due to scheduling and arranging the first and second meeting. Furthermore, it is optional for the DMSC members to receive the newsletters from the trial. The DMSC will be responsible for scheduling and arranging the meetings. Data will be provided to the DMSC at least 5 days prior to their meetings.

Interim data review

The DMSC will review non-identifiable person data for 30-day mortality at the two predetermined time points. In addition, at the second interim analysis, the DMSC will also consider available data on major lung complications defined as pneumonia and acute respiratory distress syndrome within 30 days after trauma. The DMSC can at any time request extra reviews if necessary. The data will be provided to the biostatistician in Excel. One row will represent one trial participant and each column will be a data variable. The data variables included in the raw data output are:

1: record_id (a number that uniquely identifies the patient)

2: scr_incl_randomisation (the randomisation code: group A or B)

3: outc_prim_spec___1 (occurrence of death within 30 days: 0 = no, 1 = yes)

4: outc_prim_spec___2 (occurrence of pneumonia within 30 days: 0 = no, 1 = yes)

5: outc_prim_spec___3 (occurrence of acute respiratory distress syndrome within 30 days: 0 = no, 1 = yes)

The DMSC statistician will provide aggregate data analysis for variable 3, 4 and 5 in two-by-two tables stratified on variable 2 (renamed randomisation code blinded by an external person). The data provided is only to evaluate on treatment efficacy and patient safety. Thus, no other data variables will be provided.

The DMSC may recommend stopping the trial at each of the two interim analyses if a major difference in 30-day mortality is found. There are no strict stopping criteria, but it is suggested that the recommendation should be based on only a considerable difference, such as a relative risk where the lower limit of the 95 % CI is >2 (regardless of which group is nominator). The same applies to both the first and second interim analysis. There should be no premature ending of the trial for futility before completion of the preplanned inclusion of 1420 patients with a complete 30-day follow-up.

Content of the DMSC reports

After each of the two reviews, the DMSC will produce a short report to the steering committee with recommendations for continuation, modifications, or premature termination of the trial. The DMSC will be advisory to the steering committee. Therefore, the final decision regarding potential modifications or termination will rest with the steering committee.

Members of the DMSC

Bodil Steen Rasmussen, MD, Ph.D.
Chairman of the Data Monitoring and Safety Committee
Professor
Department of Anesthesia and Intensive Care
Aalborg University Hospital

Lars Wiuff Andersen, MD, M.P.H., Ph.D., D.M.Sc.
Member of the Data Monitoring and Safety Committee
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Read and agreed by

Bodil Steen Rasmussen

Date: 20-12-2021

Signature: 

Lars Wiuff Andersen

Date: Lars W. Andersen Digitally signed by Lars W. Andersen Date: 2021.12.14 18:20:58 +01'00'

Signature:

Marius Rehn

Date: 13.12.2021

Signature: 

Brice Ozenne

Date: 19-12-2021

Signature: 

6.5 Archiving of documents

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

6.6 Funding

TRAUMOX2 is initiated by a research group of medical doctors in "Afdeling for Bedøvelse, Operation og TraumeCenter 6011, HovedOrtoCentret, Rigshospitalet, Copenhagen, Denmark". It is funded by the Novo Nordisk Foundation which is a non-profit organisation. The duration of the funding is 4 years and the amount granted is 6.326.084 DKK. It covers the sponsor's and coordinating investigator's salary, the overhead and completion costs, including that each participating centre will receive 150 euro per trial participant included with completely documented trial participants (after 30 days). Each centre will distribute the amount as agreed upon within the local organization. The Novo Nordisk Foundation is not involved in the management of the study itself, or the decision to submit the manuscript for publication, but will be mentioned in all public communication, and any publication resulting from the project will be mentioned as *"The work presented in this article is supported by Novo Nordisk Foundation grant NNF20OC0063985".* The funding will be paid to a bank account within the department in the sponsor's name. The sponsor and coordinating investigator have no conflicts of interests in relation to the Novo Nordisk Foundation. In addition, the study is also partly funded by The Lundbeck Foundation as a personal grant of 350.000 DKK to study coordinator Josefine Baekgaard. Some of this grant will be spent on salary to Baekgaard as well as unexpected expenses to the trial. Drug expenses will be covererd by the participating centres' departmental budget. Drug expenses beyond the normal department budget will also be covered by the participating centres.

6.7 Protocol changes

Can only be decided by the steering committee of the study.

Figure 1 – Participant timeline

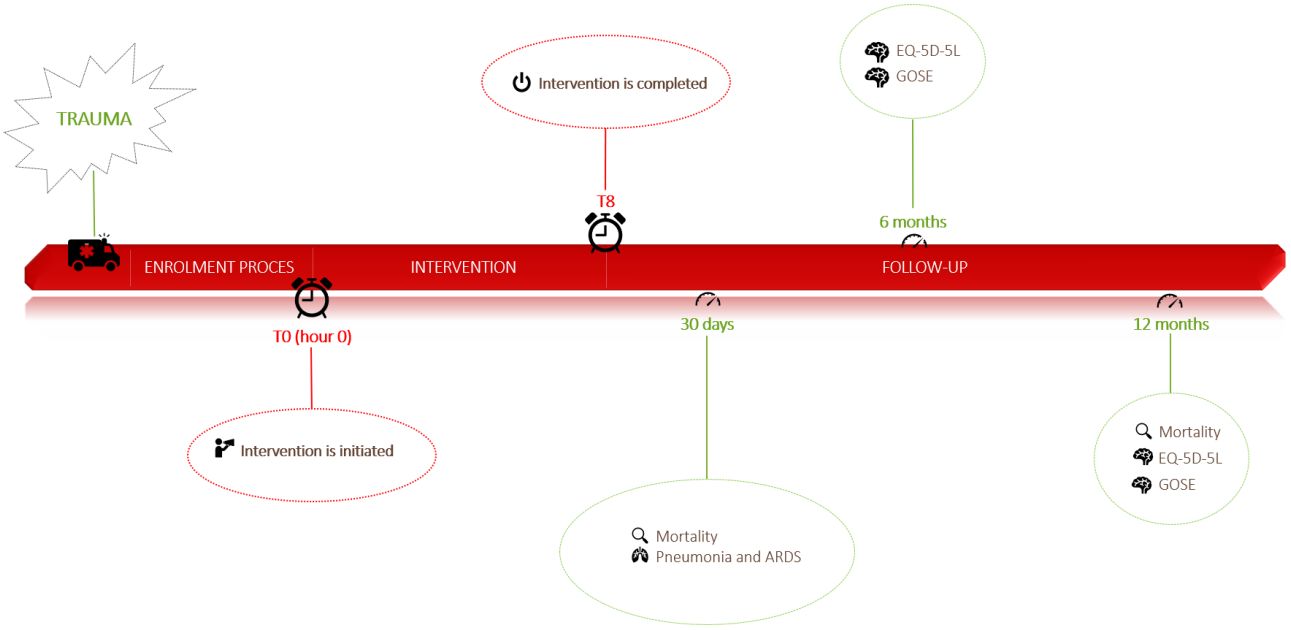
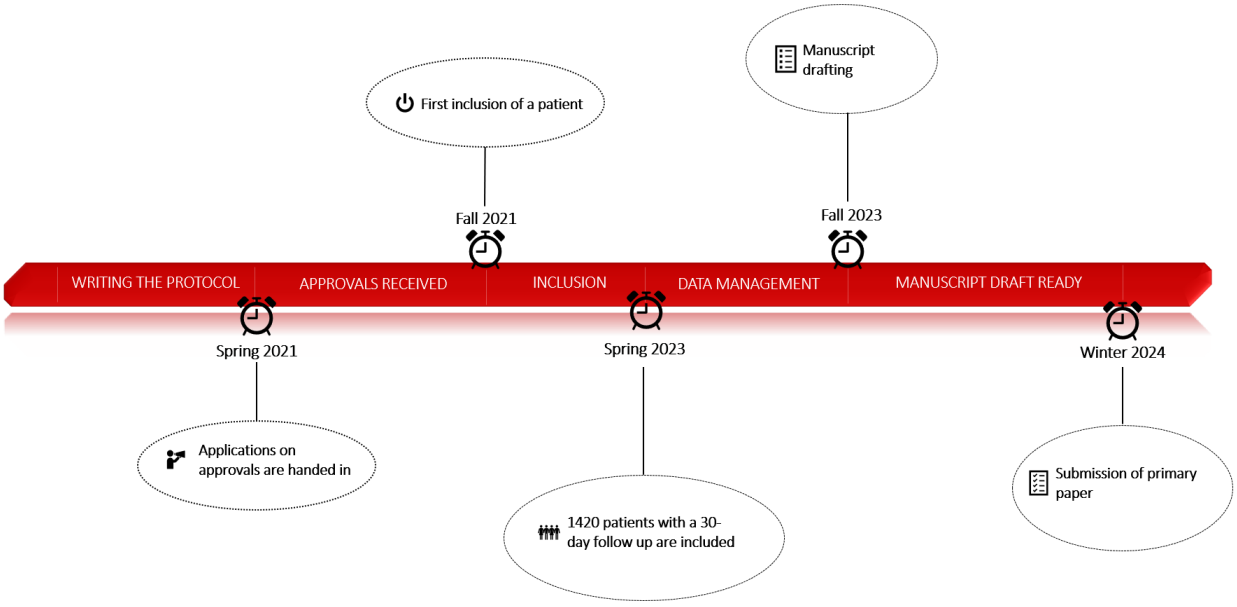


Figure 2 – Timeline of study progress



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