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.
Investigators	**Jacob Steinmetz, MD, Ph.D.** **Sponsor** Professor Afdeling for Bedøvelse, Operation og TraumeCenter, HovedOrtoCentret Rigshospitalet Den Landsdækkende Akutlægehelikopterordning Inge Lehmanns Vej 6, opgang 6, 1. sal 2100 København Ø E-mail: jacob.steinmetz@regionh.dk Phone: +45 35 45 84 34

Tobias Arleth, MD, Ph.D. student
Coordinating and primary investigator
Afdeling for Bedøvelse, Operation og TraumeCenter, HovedOrtoCentret
Rigshospitalet
Inge Lehmanns Vej 6, opgang 6, 1. sal
2100 København Ø
E-mail: tobias.arleth@regionh.dk
Phone: +45 35 45 95 02