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RESEARCH ARTICLE

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Comparing restrictive versus liberal oxygen strategies for trauma patients: The TRAUMOX2 trial—Statistical analysis plan

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Abstract

Background: The international advanced trauma life support guidelines recommend that all severely injured trauma patients receive supplemental oxygen based on very limited evidence. The TRAUMOX2 trial randomises adult trauma patients to a restrictive or liberal oxygen strategy for 8 h. The primary composite outcome consists of 30-day mortality and/or development of major respiratory complications (pneumonia and/or acute respiratory distress syndrome). This manuscript presents the statistical analysis plan for TRAUMOX2.

Methods: Patients are randomised 1:1 in variable block sizes of four, six and eight, stratified by including centre (pre-hospital base or trauma centre) and tracheal intubation at inclusion. The trial will include 1420 patients to be able to detect a 33% relative risk reduction with the restrictive oxygen strategy of the composite primary outcome with 80% power at the 5% significance level. We will conduct modified intention-to-treat analyses on all randomised patients and per-protocol analyses for the primary composite outcome and key secondary outcomes. The primary composite outcome and two key secondary outcomes will be compared between the two allocated groups using logistic regression reported as odds ratios with 95% confidence intervals adjusted for the stratification variables as in the primary analysis. A *p*-value below 5% will be considered statistically significant. A Data Monitoring and Safety Committee has been established to conduct interim analyses after inclusion of 25% and 50% of the patients.

Conclusion: This statistical analysis plan of the TRAUMOX2 trial will minimise bias and add transparency to the statistics applied in the analysis of the trial. The results will add evidence on restrictive and liberal supplemental oxygen strategies for trauma patients.

Trial Registration: EudraCT number: 2021–000556-19; ClinicalTrials.gov identifier: NCT05146700 (date of registration: 7 December 2021).

KEYWORDS
injury, oxygen, statistics, trauma, TRAUMOX2

1 | INTRODUCTION

The international Advanced Trauma Life Support (ATLS) guidelines recommend that all severely injured trauma patients receive supplemental oxygen[1] based on very limited evidence.[2,3] Thus, supplemental oxygen is commonly used in trauma patients,[4–12] although it may lead to hyperoxaemia, which has been associated with pulmonary complications and increased mortality.[13,14] The TRAUMOX2 trial[15] randomises adult patients with suspected major trauma to 8 h of a restrictive or liberal oxygen strategy. The restrictive group receives the lowest dosage of oxygen (≥21%) that ensures an arterial oxygen saturation measured by pulse oximetry (SpO_2) of 94%. The liberal group receives 12–15 L O_2/min or fraction of inspired oxygen (FiO_2) = 0.6–1.0. The primary objective of TRAUMOX2 is to compare the effect of these two oxygen strategies on 30-day mortality and/or development of major respiratory complications (pneumonia and/or acute respiratory distress syndrome [ARDS]; primary composite outcome). This manuscript presents the statistical analysis plan for TRAUMOX2.

2 | METHODS

This statistical analysis plan of the TRAUMOX2 trial has been written according to the "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials."[16] It aims to give an overview and justification of the chosen variables and statistical methods used in TRAUMOX2. The database system used for this trial is REDCap.[17] The plan is prepared while the trial is still including patients and thus before the database is exported for analysis by the trial statistician. All analyses of the primary and secondary outcomes will be conducted according to this publication. The steering committee of the trial approved this statistical analysis plan on the 11 January 2023.

The TRAUMOX2 trial has been approved by the Danish Research Ethics Committee (H-21018062), the Danish Medicines Agency (EudraCT 2021–000556-19), the Knowledge Centre on Data Protection Compliance, Health Science and Innovation in the Capital Region of Denmark and by all authorities as required at participating centres.

2.1 | Trial design

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

2.2 | Randomisation and blinding

Patients are randomised 1:1 in variable block sizes of four, six and eight, stratified by including centre (pre-hospital base or trauma centre) and tracheal intubation (yes/no) at inclusion. The randomisation table was generated outside of REDCap by a statistician otherwise not affiliated with the study. The allocation sequence list and specific block size are only known by this statistician and will remain concealed from the investigators. Prior to randomisation, consent must be obtained either by proxy (from another physician) or according to national legislation. Immediately afterwards, randomisation is done by opening a concealed envelope with information on allocation. Each concealed envelope contains a study ID that matches a study ID on the randomisation list generated by the statistician. Subsequently, informed consent is confirmed from the patient or a relative in case the patient cannot give consent. National law on consent is followed if neither the patient nor the relative can provide consent. A more detailed description of the consent procedure is presented in the protocol and on the study website.[15,18]

The treating staff will be aware of the patients' randomisation group, and due to the nature of oxygen treatment, patients and relatives will often be aware of the allocated oxygen strategy as well. While the trial is including patients for the study, members of the research team will also be aware of the patients' oxygen allocation strategy. At least two allocation-blinded primary outcome assessors (specialists in anaesthesia, intensive care and emergency medicine or similar) will be appointed at each centre to assess in-hospital lung complications (pneumonia and/or ARDS). Blinding will be ensured by concealing all information indicative of the allocation prior to assessment. The trial statistician is blinded to the allocation of treatment, and manuscript writers will become blinded to the allocation of treatment once the trial ends and data are exported for analysis. In the exported dataset, the randomisation groups will be renamed A and B by an unblinded research assistant otherwise not affiliated with the study. Afterwards, the renamed dataset will be forwarded to the trial statistician for data analysis. While data are analysed, the blinded authors will write two versions of the manuscript: one where treatment A is the liberal oxygen strategy and another version where treatment A is the restrictive oxygen strategy. These two manuscripts will exclude data on oxygenation during the intervention period, as this would reveal the allocation group. All authors must agree on both versions before unblinding.

2.3 | Sample size calculation

In TRAUMOX1,[19] the pilot study for TRAUMOX2, the primary composite outcome occurred in 20% in the restrictive group and 33% in the liberal group. In larger studies, mortality from major trauma has been estimated to be 6%–12%,[20] and the incidence of ventilator-associated pneumonia post trauma was almost 30% in one study.[14] In TRAUMOX2, we estimate that with 710 trial participants in each trial arm, including a drop-out rate of 3.5%, yielding a total of 1420 patients, we will be able to detect a 33% relative risk reduction in the incidence of the composite primary outcome (30-day mortality and/or major respiratory complications) 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 and 10% in the restrictive group. This corresponds to an absolute between-group difference of 5% points.

TABLE 1 Baseline registrations

Variable	Definition
Age	Calculated from birth (year)
Sex	Genotypic
Height	Measured in centimetre
Weight	Measured in kilogram
Active smoker (yes/no)	
Comorbidities prior to trauma (yes/no)	
Lung disease	Chronic obstructive pulmonary disease, asthma, lung fibrosis or positive COVID-19 test on the day of admission and other
Cardiovascular disease	Hypertension, angina, atrial fibrillation, heart failure, coronary artery disease and other
Other	
Mechanism of injury[a]	Traffic (motor vehicle accident, motorcycle accident, bicycle accident, pedestrian and other), shot, stab, struck, fall (0–2, 2–4 and >4 m), blast/explosion, other and unknown
Dominating type of injury	Blunt or penetrating
Site of inclusion	Pre-hospital or in-hospital
Airway at inclusion[b]	Non-intubated or intubated
Use of pre-hospital or in-hospital supplemental oxygen prior to randomisation (yes/no)	
Highest SpO_2 measured prior to randomisation	Number
Time with supplemental oxygen treatment before randomisation	Minutes
Indication for supplemental oxygen treatment before randomisation	Life-saving (SpO_2 <85%), avoiding hypoxaemia (SpO_2 < 90%) and routine treatment independent of SpO_2
Supplemental oxygen administration form before randomisation	Nasal cannula, non-rebreather mask and intubated
Initial oxygen flow or initial FiO_2	Number
Receiving trauma centre	Rigshospitalet, Copenhagen, Denmark
	Odense Universitetshospital, Odense, Denmark
	Aarhus Universitetshospital, Aarhus, Denmark
	Erasmus Medical Centre, Rotterdam, The Netherlands
	University Hospital Bern, Switzerland
Active treatment of pneumonia on admission (yes/no)	Evaluated through patient medical charts
Intubation (yes/no)	Pre-hospital, trauma centre
Death	Pre-hospital, trauma centre
Pre-hospital information	
First vital signs[c]	
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
Pulse	bpm
Respiratory rate	Number/min
SpO_2	Number
Body temperature	Degree Celsius
Glasgow Coma Scale score	Number 3–15
Trauma centre information	
Type of transport to the trauma centre	Ground ambulance, helicopter, combination of ground ambulance and helicopter, private vehicle, walk-in, police and other
Time from trauma to trauma centre arrival	Minutes
Surgery performed in the trauma centre (yes/no)	

(Continues)

TABLE 1 (Continued)

Variable	Definition
If yes, type of surgery	Neurosurgery, cardiothoracic surgery, abdominal surgery, orthopaedic surgery, urological surgery, vascular surgery, gynaecological surgery and other
First vital signs[b]	
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
Pulse	bpm
Respiratory rate	Number/minute
SpO_2	%
Body temperature	Degree Celsius
Glasgow Coma Scale score	Numbers 3–15
Destination after trauma centre resuscitation	Operating room, intensive care unit and ward
Injury details	
Injured body region(s)	Head, neck, face, spine, thorax, abdomen, pelvis, extremity and other(s)
Abbreviated injury score codes	Numbers
Injury severity score	Number

Abbreviations: FiO_2, fraction of inspired oxygen; SpO_2, arterial oxygen saturation measured by pulse oximetry.
[a]Following the Utstein template for reporting mechanism of injury.[33]
[b]A supraglottic airway is also considered intubation and can be noted in the case report form separately.
[c]Including time and date of vital sign measurement.

2.4 | Framework

The primary analysis will be conducted as a superiority trial to test whether the restrictive group is superior to the liberal group.

2.5 | Statistical interim analysis and stopping guidance

An independent Data Monitoring and Safety Committee (DMSC) has been set up. The committee includes a statistician. The committee met when information on 30-day mortality had been collected in 355 patients (~25% of the envisioned sample size) and recommended the trial to continue. The DMSC will meet again when 30-day mortality has been collected in 710 patients (~50% of the sample size estimation). In addition, at the second interim analysis, the DMSC will also consider available data on major respiratory complications. Prior to the meetings, the DMSC statistician performs an interim analysis with data blinded towards the allocation. There are no strict stopping criteria, but in the DMSC charter, it is suggested that a recommendation should be based on only a considerable difference, such as a relative risk where the lower limit of the 95% confidence interval (CI) is >2 (regardless of which group is nominator). This applies to both the first and second interim analysis. There will be no pre-mature ending of the trial for futility before the pre-planned inclusion of 1420 patients. In addition, the sponsor has the responsibility to report the overall number of annual Serious Adverse Events to the committee. The DMSC will have an advisory role to the steering committee and therefore the final decision regarding potential modifications or termination will rest with the steering committee. Detailed information on the DMSC is available on the study website (www.traumox2.org).

2.6 | Timing of outcome assessments and final analysis

The registered variables at baseline, during intervention and during admission (in-hospital) are presented in Tables 1, 2 and 4. In addition to the variables collected during the intervention (Table 2), a figure displaying the median hourly SpO_2 with interquartile range (IQR) for both groups will be made. The primary composite outcome and key secondary outcomes are presented in Table 3. The exploratory secondary outcomes at day 30 are available in Table 4. A long-term follow-up is assessed at 6 and 12 months on morbidity and quality-of-life outside the scope of the primary analysis. A 12-month mortality will also be assessed. The primary analysis can begin 30 days after the last patient has been included.

3 | STATISTICAL PRINCIPALS

3.1 | CIs and *p*-values

We will use a significance level of 5% and thus 95% CIs on our estimates. Significance tests will be two sided. The exploratory secondary outcomes will be adjusted for multiple testing by having their *p*-values, and thus 95% CIs, assessed using a significance level lower than 5% according to the Benjamini–Hochberg method.[21] Hence, for the *p*-values of the exploratory secondary outcomes, it will be indicated whether they are significant while controlling the false discovery rate at 5%.

TABLE 2 Data collected specifically during intervention period

Variable	Definition
Time from trauma to randomisation	Minutes
For every hour during the 8-h intervention:	
Patient location	Pre-hospital, trauma centre, operating room, examination room, post-anaesthesia care unit, intensive care unit and ward
SpO_2	Median
Type of supplemental oxygen	None, nasal cannula, non-rebreather mask and intubated[a]
Oxygen flow (L/min)	Median
FiO_2	Median
First ABG[b] (at hour 1 ± 30 min after randomisation)	
PaO_2	kPa or mmHg
Haemoglobin	mmol/L
Lactate	mmol/L
Second ABG[b] (at hour 6 ± 2 h after randomisation)	
PaO_2	kPa or mmHg
Haemoglobin	mmol/L
Lactate	mmol/L
Major protocol violation[c] (yes/no)	
Protocol deviation (yes/no)	

Abbreviations: ABG, arterial blood gas; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen tension; SpO_2, arterial oxygen saturation measured by pulse oximetry.
[a]A supraglottic airway is also considered intubation and can be noted in the case report form separately.
[b]Arterial blood gas.
[c]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 O_2/min AND SpO_2 ≥98% recorded at two consecutive hourly time points on the data collection sheet. For intubated trial participants: FiO_2 >0.4 AND SpO_2 ≥98% recorded at two consecutive hourly time points on the data collection sheet. Liberal O_2 group, during the intervention period. For non-intubated trial participants: Supplemental oxygen <3 L O_2/min at two consecutive hourly time points on the data collection sheet. For intubated trial participants: FiO_2 <0.4 at two consecutive hourly time points on the data collection sheet.

3.2 | Adherence and protocol deviations

For all TRAUMOX2 trial participants, it is possible to deviate from the protocol if clinically justified by the treating physician. These reasons should always be documented in REDCap.

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 O_2/min AND SpO_2 ≥98% recorded at two consecutive hourly time points on the data collection sheet.

For intubated trial participants: FiO_2 >0.4 AND SpO_2 ≥98% recorded at two consecutive hourly time points on the data collection sheet.

- Liberal O_2 group, during the intervention period

TABLE 3 Primary outcome and key secondary outcomes

Primary outcome	Definition
30-day mortality and/or development of major respiratory complications (pneumonia[a] and/or acute respiratory distress syndrome (ARDS)[b]) (yes/no)	Assessed by two specialists in anaesthesia, intensive care medicine, emergency medicine or similar using blinded medical records, laboratory and microbiology results and radiological assessments
Key secondary outcomes	
30-day mortality (yes/no)	
Major respiratory complications (pneumonia and/or ARDS) within 30 days (yes/no)	

Note: All key outcomes are accompanied by specific times and dates.
[a]Pneumonia is categorised as non-ventilator-associated pneumonia (PNEU) or ventilator-associated pneumonia (VAP), defined by the Centers for Disease Control and Prevention (CDC) criteria.[24]
[b]ARDS is categorised as mild, moderate or severe, defined by the Berlin definition.[25]

For non-intubated trial participants: Supplemental oxygen <3 L O_2/min at two consecutive hourly time points on the data collection sheet.

For intubated trial participants: FiO_2 <0.4 at two consecutive hourly time points on the data collection sheet.

For the main article, data on protocol deviations and major protocol violations will be presented in Table 2.

3.3 | Analysis populations

We will conduct modified intention-to-treat analyses on all randomised patients.[22] The modification is based on the exclusion criterion stating that trauma patients are secondarily excluded after randomisation and trauma centre diagnostics (e.g., secondary survey after computed tomography scan), if the latter has resulted in expected discharge within 24 h (due to few or no injuries). If consent is withdrawn for a patient, no data after the day will be collected (Figure 1). Per-protocol analyses will also be carried out, but only for the primary composite outcome and key secondary outcomes. The per-protocol population is the same as the modified intention-to-treat population with exclusion of those having one or more major protocol violations.

4 | TRIAL POPULATION

4.1 | Screening, eligibility and recruitment

Screening, eligibility and recruitment is conducted as stated in the trial protocol.[15] A CONSORT[23] flow diagram is presented in Figure 1.

TABLE 4 Exploratory secondary outcomes (in-hospital)

Variable	Definition
Initial surgery duration after trauma centre treatment	Minutes
Referring ward after initial surgery after trauma centre treatment	Intensive care unit and ward
Intensive care unit admission (yes/no)	
Brain injury within 7 days of admission (yes/no)	Including description based on the patient's medical record
Myocardial infarction within 7 days (yes/no)	
Cerebral ischaemia within 7 days (yes/no)	
Episodes of hypoxaemia (yes/no)	Number of times with SpO_2 <90% in the data collection sheet
Intubation post-randomisation (yes/no)	During and after intervention
If yes, location, time and date of intubation	Pre-hospital, trauma centre, intensive care unit Mechanical ventilation initiated as part of general anaesthesia on spontaneously breathing patients to facilitate surgery is not included
Extubation (yes/no)	
Re-intubation (yes/no)	
Total number of intubations within 30 days	Number
Time on mechanical ventilation (hours)[a]	Number of ventilator hours within 30 days after enrolment
Days alive without mechanical ventilation (days)	Number of ventilator-free days within 30 days after enrolment
Days alive outside the intensive care unit within 30 days	Number
Intensive care unit length of stay	Days
Intensive care unit re-admission(s) (yes/no)	
Hospital length of stay[b]	Days
Sepsis during hospital admission (yes/no)	Clearly stated in the patient's medical record by a physician or assigned as a diagnosis
Pneumonia post-discharge within 30 days after enrolment (yes/no/patient still admitted after 30 days)	Evaluated through drugs prescribed after hospital discharge in countries where this information is available
Surgical site infection(s) within 30 days (yes/no)	At least one of the following: purulent drainage, positive microbiologic testing from surgical site/wound and sign(s) of infection, diagnosis of surgical site infection by a surgeon

[a]Mechanical ventilation initiated on spontaneously breathing patients to facilitate surgery is not included.
[b]Only the primary admission will be considered (no re-admissions). If a patient is transferred from the hospital to a psychiatry department or a rehabilitation centre for further treatment, then the day of transfer is considered the date of hospital discharge.

4.2 | Baseline patient characteristics

Baseline variables for all analysed patients are presented in Table 1. Data will be summarised with numbers and percentages for categorical variables and medians with IQRs for continuous variables. According to the CONSORT 2010 statement,[23] differences in baseline variables between the restrictive oxygen group and liberal oxygen group will not explored.

4.3 | Withdrawal and follow-up

Since this is an acute medical study, patients are always included upon the discretion of an including physician. Patient or next-of-kin consent is sought after inclusion in all cases. After inclusion, patients are at any time allowed to refrain from giving consent or withdraw consent they have given previously. If consent is withdrawn, patients are followed up until this time point. However, the participating centres' individual approach will always be according to national law.

5 | ANALYSIS

5.1 | Outcome definitions

5.1.1 | Primary outcome and key secondary outcomes

The primary outcome is a composite outcome consisting of 30-day mortality and/or major respiratory complications (pneumonia and/or ARDS) within 30 days. The 30-day mortality is assessed using in-hospital or national/local registries. Whenever this is not possible, for instance if the patient is a foreigner, 30-day mortality will be sought by contacting the patient or relatives by phone or e-mail on day 30 after inclusion or later. At least three attempts on three

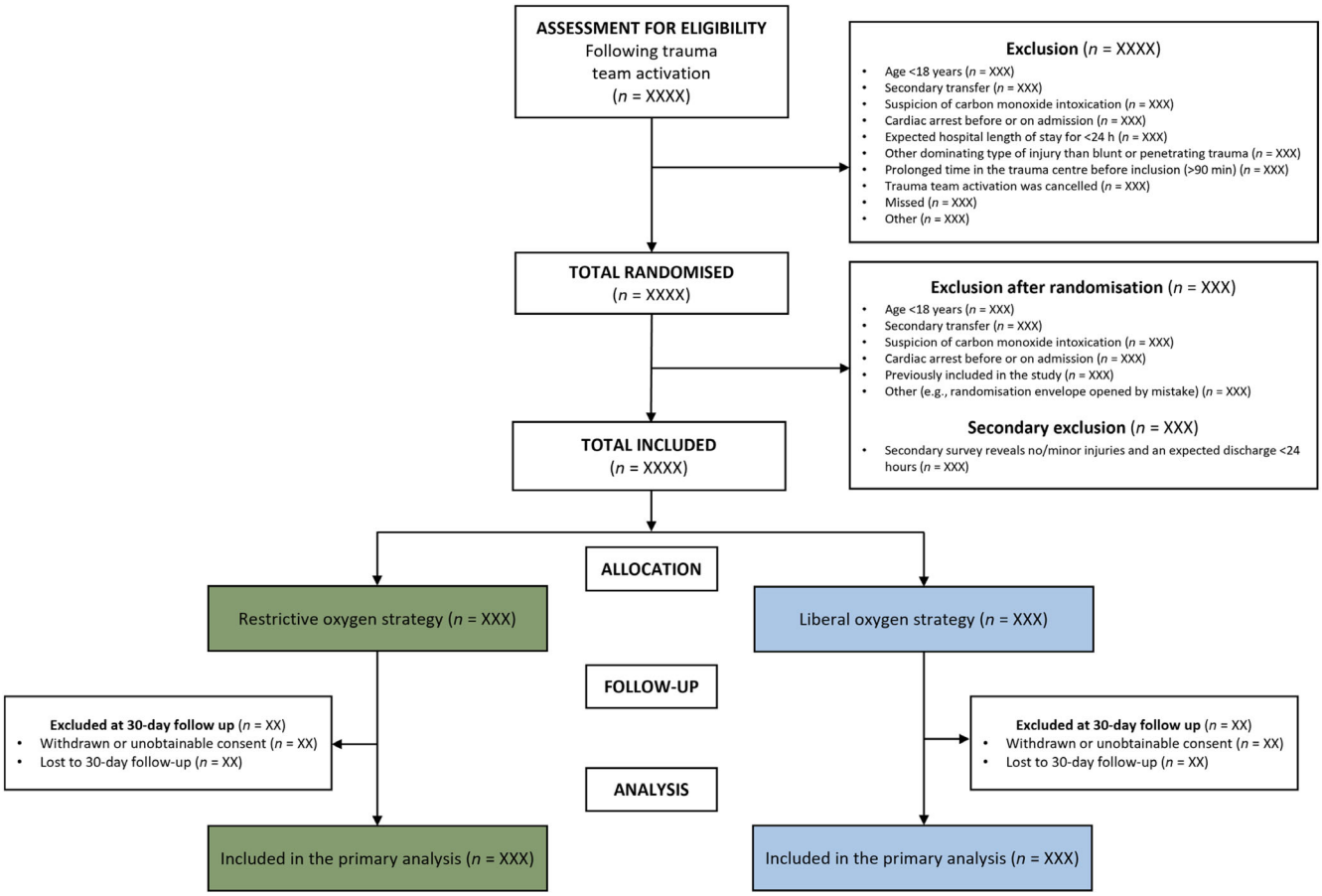

FIGURE 1 CONSORT flow diagram of screening, randomisation and follow-up.

different days should be carried out. If no contact is obtained, and the patient was discharged to home from either the TRAUMOX2 including hospital or a subsequent receiving hospital, the patient is considered to be alive on day 30. However, if the patient was transferred to another hospital without medical record access for TRAUMOX2 investigators, 30-day vital status is considered unknown and 30-day mortality is then considered as missing data. The definition of major respiratory complications, pneumonia and ARDS, is in accordance with the criteria described by the Centers for Disease Control and Prevention (CDC)[24] and the Berlin definition,[25] respectively. It is evaluated through the available medical record system via a blinded assessment by at least two specialists in anaesthesia, intensive care medicine, emergency medicine or similar appointed at each centre. If the patient is transferred to another hospital and the medical record from that hospital until day 30 is not available, the assessment will be based on the available medical record from the TRAUMOX2 participating centre only. However, an attempt of obtaining the medical record of the receiving facility will be carried out and will be included in the primary outcome assessment if possible.

The two key secondary outcomes are 30-day mortality and major respiratory complications (pneumonia and/or ARDS) within 30 days, respectively.

The details of all primary and key secondary outcomes are presented in Table 3.

5.1.2 | In-hospital registrations and exploratory secondary outcomes

Additional outcomes are presented in Table 4.

5.2 | Analysis methods

5.2.1 | Primary composite outcome

The primary composite outcome will be compared between the two groups using logistic regression and reported as odds ratio (OR) with 95% CI, adjusted for the stratification variables. An additional analysis for the primary composite outcome using logistic regression will be made with adjustment for the stratification variables, age, sex, injury severity score and the first available Glasgow Coma Scale score after trauma. Excess association within the stratification is adjusted for through the method of generalised estimating equations (GEE) the including base as a clustering variable. Potential differential dropout

from the study—through late withdrawal of consent or unreachable for follow-up—is adjusted for through weighting of the available data by the inverse of the probability of being observed[26]; the latter are estimated in a logistic regression model on baseline characteristics and the allocation. Adjustment of the variance matrix to reflect the weighting is included in the GEE method. Evaluation of significance will be based on the *p*-value.

5.2.2 | Key secondary outcomes

The key secondary outcomes will be analysed similarly to the primary composite outcome and adjusted for the same covariates.

5.2.3 | Exploratory secondary outcomes

Exploratory secondary outcomes will be analysed similarly to the primary composite outcome and adjusted for the same covariates while the type of regression is according to the type of the outcome (e.g., logistic regression for binary outcomes and linear regression for continuous outcomes). Evaluation of significance will be adjusted according to the Benjamini–Hochberg method.[21]

5.2.4 | Subgroup analyses

The following subgroup analyses related to the primary outcome will be performed:

- Initially intubated within 1 h after trauma
- Intensive care unit admission
- Moderate or severe traumatic brain injury (abbreviated injury score ≥3)
- Known lung disease
- Episode(s) of hypoxaemia during the intervention (SpO_2 <90%)
- Included pre-hospital versus in-hospital
- Injury severity score >15

5.3 | Missing data

If patients withdraw their consent once they regain consciousness, data up until that day are collected and stored. However, the participating centres' individual approach will always be according to national law. If data are available for time-dependent outcomes (e.g., outcomes that are specified to be assessed 7 or 30 days after inclusion), the assessments will be done dependent on the timing of withdrawal of consent. In case a time-dependent outcome occurs within the period of available data for patients who withdraw consent, the outcome will be registered. If an outcome does not occur within the period of available data for a time-dependent outcome, the outcome is registered as missing data. Missing outcome data, which primarily covers the patients who withdraw consent, are adjusted for using the inverse probability weighting method described above under primary composite outcome.

5.4 | Additional analyses

A statistical analysis plan for the long-term follow-up at 6 and 12 months will become available on the study website (www.traumox2.org).

5.5 | Harms

5.5.1 | Adverse events and serious adverse events

We have chosen to register only atelectases assessed by a radiologist and irritability of airway mucosa only if registered by the health care staff in the medical record as adverse events in accordance with established practise in trials on critically ill patients who experience many events as part of the natural trajectory of the primary disease process or expected as a result of the critical illness.[27] For the main article, the numbers and frequencies will be presented as shown in the Table S1.

5.6 | Statistical software

SAS (version 9.4) will be used for all analyses.

6 | DISCUSSION

The trauma population is particularly exposed to high concentrations of oxygen,[5,7–9] although the supporting evidence is extremely sparse.[2,3] The TRAUMOX2 trial will add important scientific information to this area. The aim of this statistical plan is to provide transparency of the statistics that will be used to evaluate the data. The plan has been prepared according to current recommendations[16] and presented before the last patient has been randomised.

Randomisation is carried out with sealed envelopes stratified by intubation at inclusion and the including centre or pre-hospital base. This simple solution was chosen to avoid randomisation challenges in the acute setting where no internet connection may be available, for example on the road or in the air, and to make randomisation quicker and more pragmatic. However, there is a risk, through reshuffling of the envelopes or dispersion over multiple vehicles related to a pre-hospital base, that the generated allocation sequence is not strictly followed. This would reduce the efficiency of the block randomisation slightly as allocation may thus be less balanced, but randomisation is not invalidated as any reshuffling is independent of the actual allocation.

The rationale for choosing our primary composite outcome, 30-day mortality and/or development of major respiratory

complications (pneumonia and/or ARDS), falls into two categories. First, both outcomes are patient-centred and important for the trauma patient; trauma is the leading cause of death globally for people up till 49 years of age[28] and the incidence of pneumonia is high amongst critically ill patients and lung complications are associated with longer hospital stays and increased morbidity and mortality.[29–31] Second, a primary composite outcome can increase the statistical precision and thus the efficiency of the trial.[32] Furthermore, the primary outcome is assessor-blinded to compensate for the open-label intervention. Finally, the numbers from the literature on mortality and pneumonia in trauma patients that were chosen for the sample size calculation were based on the best available evidence including a pilot trial when the trial was designed.

We have chosen logistic regression for our primary outcome because it is the natural choice of statistical model in which to analyse binary outcomes. The effect estimates obtained are ORs that are not dependent on the marginal distribution of the outcome and, as such, may be directly compared to OR effect estimates from similar studies but on patients with higher or lower risk. Also, we will assess the significance of our exploratory secondary outcomes controlling for the false discovery rate at 5% with the Benjamini–Hochberg method, which yields a lower Type-I error in our study.[21]

The primary challenge in the statistical analyses is the adjustment for possible differential attrition. Several outcomes cannot, or only partly, be evaluated because of loss to follow-up, withdrawal of consent or death. For example, a person who dies 3 days after trauma has automatically a lower chance of developing pneumonia and only a maximum of 3 days intensive care unit stay. As the intervention is hypothesised to have an effect on, amongst other things, mortality, this probable differential attrition is to be taken seriously. We adjust for differential attrition by inverse probability weighting.[26]

7 | DISSEMINATION

The data on the primary composite outcome, key secondary outcomes and exploratory secondary outcomes will be analysed when 30-day follow-up is complete. The data presented in this manuscript will constitute the basis for the primary publication of the study, which will be submitted to a peer-reviewed clinical journal. The data on the long-term follow-up at 6 and 12 months will be presented in separate publications submitted later to peer-reviewed clinical journals when the long-term follow-up is complete. All results will be sought published, including both positive, negative or inconclusive results.

8 | STATUS

The TRAUMOX2 trial began recruiting the 7 December 2021. As of 11 February 2023, 913 patients have been included. We expect that the last patient is included in the beginning of year 2024.

AUTHORS' CONTRIBUTIONS

TA and JB drafted the manuscript according to statistical analysis plan guidelines in close collaboration with LSR, JS and VS. MK and JH made substantial scientific contributions to the manuscript. All authors have read and approved the final manuscript for publication. TA, JB, MK, JH, LSR and JS are members of the TRAUMXO2 trial steering committee. VS is the statistician of the TRAUMOX2 trial. JS is the sponsor and chief investigator of the trial and TA is the coordinating investigator of the trial.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data is generated for this publication thus there is no need for a data availability statement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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