Protocol

Version 1.0

The impact of initial restrictive versus liberal oxygen strategies after chest trauma – a secondary analysis of the randomised, controlled TRAUMOX2 trial

Date: 28.01.2025

Study registration

EudraCT number: 2021-000556-19

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General information

Protocol title: The impact of initial restrictive versus liberal oxygen strategies after chest trauma – a secondary analysis of the randomised, controlled TRAUMOX2 trial

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Abbreviations

AE	Adverse Events
AIS	Abbreviated Injury Scale
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Intervals
DAOOH	Days Alive Out Of Hospital
FiO2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
ICU	Intensive Care Unit
ISS	Injury Severity Score
LOS	Length of Stay
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Events
SpO2	Blood Oxygen Saturations
TBI	Traumatic Brain Injury

Appendices (as applicable in Denmark)

1. Deltagerinformation til forsøgsperson
2. Samtykkeerklæring til forsøgsperson
3. Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt
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5. Consent form to the study participant

1. Background and rationale

Traumas and injuries are common and represent the main cause of mortality in the younger population(1). Traumas can cause disability and may thus lead to a major impact on public health(2). Chest trauma is common in the multi-traumatised patient(3). The injuries can manifest in many ways, including pulmonary contusion, rib fractures, atelectasis, pneumothorax, haemothorax, spinal fractures, diaphragmatic injuries, and tracheobronchial injuries(4). Pulmonary injuries can be caused by both direct trauma towards the thorax and as indirect injuries from the inflammation following injuries to other body regions, including traumatic brain injury (TBI)(5,6). Blunt trauma is the most common trauma mechanism for direct trauma towards the thorax, and lung failure related to traumatic thoracic lesions have been associated with an increase in-hospital and intensive care unit (ICU) length of stay (LOS) regardless of age along with increased mortality with higher age(4,7).

Emergency personnel follows the Advanced Trauma Life Support (ATLS) guideline in the initial phase of trauma treatment(8). These guidelines recommend supplemental oxygen for all severely injured trauma patients, but the guideline do not provide recommendations on an upper limit of the amount of oxygen supply nor a maximum fraction of inspired oxygen (FiO2). A systematic review and meta-analysis with focus on acutely ill patients compared a restrictive oxygen strategy with a liberal oxygen strategy. They included 23 trials and found a higher mortality both in-hospital and at longest follow-up in the liberal oxygen group(9). Others have found no difference in mortality for ICU patients when comparing a restrictive and a liberal oxygen strategy(10). However, a systematic review on oxygen treatment for trauma patients have found evidence to be extremely sparse(11), while systematic reviews of the effects of a higher versus a lower oxygen treatment for ICU patients, including long-term consequences, find evidence to be uncertain and the certainty of evidence to be low to very low(12,13).

Different ventilatory regimens are suggested for treatment and prevention of pulmonary complications following traumatic thoracic lesions, and whether non-invasive ventilation or mechanical ventilation is appropriate is a matter of debate and may differ in the individual case(4,14). Several studies have been performed in critically ill patients regarding lung protective ventilation and a lower tidal volume seems to be beneficial(6,15,16). However, some suggest that these strategies cannot be directly extrapolated to the acute trauma treatment(17).

The TRAUMOX2 trial, an international, multicentre, randomised, controlled trial, compared a restrictive versus a liberal oxygen strategy for the first 8 hours after trauma(18). Participants were evaluated for 30-day mortality and/or major pulmonary complications (pneumonia or acute respiratory distress syndrome (ARDS)) within 30 days as a composite primary outcome and found no significant difference between the two groups. The trial included participants with thoracic lesions among other patient groups. In this substudy of the TRAUMOX2 trial, we aimed to investigate the participants with traumatic thoracic lesions comparing the two oxygen strategies.

1.1 Objectives

The objective of this substudy was to assess if a restrictive versus a liberal oxygen strategy within the first 8 hours after trauma affects the number of days alive out of hospital (DAOOH) until day 30 for trauma patients with thoracic lesions.

Hypothesis

We hypothesized that trauma patients with thoracic lesions allocated to a restrictive oxygen strategy would have more DAOOHs at 30 days after trauma compared with patients allocated to a liberal oxygen strategy.

1.2 Trial design

An international, multicentre, parallel-grouped, superiority, open-label, randomised, controlled, clinical trial.

2. Methods: Participants, intervention, and outcomes

2.1 Study setting

This was a substudy on the TRAUMOX2 trial(19). Participants were included in Denmark, the Netherlands, and Switzerland, participating centres are listed under the study sites. Data were collected within each centre. This protocol was written according to the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 guideline(20) and supplemented with a detailed statistical analysis section. The combined protocol with a statistical analysis plan was uploaded to the TRAUMOX2 website (www.traumox2.org).

2.2 Eligibility criteria

2.2.1 Inclusion criteria

- Included in the TRAUMOX2 trial
- Thoracic lesions defined as Abbreviated Injury Scale (AIS)* thorax≥1

**We used The Abbreviated Injury Scale 2005 revision, 2008 update, AAAM*(21)

2.2.2 Exclusion criteria

- Secondary exclusions from TRAUMOX2(19)

2.3 Interventions

The participants were randomised to receive either a restrictive or a liberal oxygen treatment for 8 hours after randomisation(19).

2.4 Outcomes

2.4.1 Primary outcome

Days alive and out of hospital at 30 days after randomisation.

2.4.2 Secondary outcomes

- 30-day mortality
- Hospital LOS
- Major respiratory complications (ARDS and/or pneumonia) within 30-days
- Days alive without mechanical ventilation within 30 days
- 1-year mortality

2.5 Recruitment

Participant recruitment was conducted according to the process described in the TRAUMOX2 protocol(19) and always according to national rules and laws in the specific country.

2.6.1 Withdrawal

The trial participant's/trial participant's next-of-kin consent could be withdrawn at any time for any reason in accordance with the Helsinki Declaration(22). Likewise, trial participants could be withdrawn from the trial at any time by an investigator. The reason for withdrawal was recorded in the electronic Case Report Form. A majority of the including sites were allowed to use data up until the date of withdrawal if a participant or their relatives declined consent or withdrew consent after intervention was initiated.

3. Methods: Assignment of interventions

3.1 Allocation

Participants were included in the TRAUMOX2 trial and randomized to the intervention group (restrictive oxygen strategy) or the control group (liberal oxygen strategy) as described in the trial protocol(19). The treatment was continued for 8 hours after initiation.

3.2 Blinding

Treating staff was aware of the participant's allocation group. The research team was aware of the randomisation allocation while including patients for the study, during the intervention, and while collecting data. Allocation was not kept concealed for the participants during intervention. Statistician and authors for this substudy was not blinded for treatment allocation when performing analyses and manuscript drafting.

4. Methods: data collection, management, and analysis

4.1 Data collection methods

Data for this substudy was requested from the TRAUMOX2 database and included the following data points:

- Hospital and ICU LOS
- Mechanical ventilation (yes/no)
- Type of oxygen delivery during intervention (none / nasal cannula / non-rebreather mask / intubated)
- In-hospital variables (AIS, Injury Severity Score (ISS), pneumonia, ARDS, other infections (surgical site infection or sepsis))
- Adverse Events (AE) and Serious Adverse Events (SAE)
- Co-morbidities prior to trauma: Categorised in heart disease, pulmonary disease, other diseases, psychiatric co-morbidity
- Active smoker (yes/no)
- Specifics of possible brain injury (type and extent) and other cerebral complications such as cerebral ischemia
- Date of death

4.2 Data management

TRAUMOX2 data was stored in an electronic, secure, web-based, centralised system - REDCap(23). The REDCap database was set up from Rigshospitalet in the Capital Region, Denmark. The electronic case report form (eCRF) was digital.

4.3 Statistical methods

4.3.1 Sample size and power

A total of 1,508 participants completed the TRAUMOX2 trial. Of these, 728 participants were registered with AIS thorax≥1. Average LOS in the TRAUMOX2 trial population was 12 days with a standard deviation of 14. We estimated an average of 17 days alive and out of hospital in the liberal arm of our study population. With a power of 80% and a 5% significance level, we were able to detect an increase to 20 days alive and out of hospital in the restrictive group. This corresponds to an absolute difference of 3 days.

4.3.2 General analytical principles

Our primary analysis was carried out as an intention-to-treat analysis. Additionally, we performed a per-protocol analysis, only including participants with no major protocol violations according to the definitions in the TRAUMOX2 protocol(19). Results were presented with 95% confidence intervals (CI). Significance tests were two-tailed and a p-value less than 0.05 was considered significant. Multiple testing was adjusted for using the Benjamini-Hochberg method(24).

A biostatistician performed the statistical analyses.

4.3.3 Missing data

All eligible participants were included in the analyses. We used inverse probability weighting to adjust for potential differential attrition. These weights were calculated from a logistic regression including site of inclusion, status of tracheal intubation upon inclusion, age, sex, ISS, first available GCS score after trauma, allocation, the dominating injury type, the type of oxygen supply, psychiatric comorbidity and (for Danish patients) whether a personal identification number was registered, or the use of a temporary personal identification number.

4.3.4 Statistical analyses

The primary outcome was DAOOH at day 30 and was compared between the two groups by the group medians. This comparison was adjusted for the stratification variables, site of inclusion and status of tracheal intubation upon inclusion, by weighing the medians using propensity score weights. These weights were calculated in a logistic regression model of randomisation group allocation on the stratification variables. P-values and 95% CIs were estimated from the empirical distribution of 10,000 multilevel bootstrap replicates of the data for which first sites, and thereafter patients within sites were sampled with replacement. Propensity scores and the weights to adjust for potential differential attrition were recalculated within each bootstrap replicate.

Additionally, a similar analysis adjusting for the stratification variables, and the variables age, sex, ISS, dominating injury type, pulmonary disease prior to trauma, and smoking status was performed.

Secondary continuous outcomes were analysed similarly to the primary outcome and adjusted for the same stratification variables. Secondary binary outcomes were compared between the two randomisation groups using multivariable linear regression with a binomial error term, adjusted for the stratification variables, and reported as risk difference (RD) with corresponding 95%CIs. Clustering of patients within sites and weighing to adjust for potential differential attrition was adjusted for through generalized estimating equations.

4.3.5 Subgroups
Subgroups included:

- ICU admission (yes/no)
- Intubated at randomisation (yes/no)
- Enrolled prehospital vs. in-hospital
- ISS>15
- Severe chest trauma (thorax AIS ≥3)
- Moderate to severe chest trauma (thorax AIS ≥2)
- Mild chest trauma (thorax AIS=1)
- Active smoker (yes/no)

4.3.6 Major protocol violations
No major protocol violations were defined for the follow-up study. Major protocol violations in the TRAUMOX2 trial are registered in the study protocol(19).

5. Methods monitoring

5.1 Data monitoring
The TRAUMOX2 trial was monitored as described in the publication(18).

All investigators of the trial handled information confidentially.

6. Ethics and dissemination

6.1 Research ethics approval
The randomised, controlled trial of TRAUMOX2 was conducted in compliance with the Helsinki Declaration in its latest version(22), the Good Clinical Practice (GCP) guidelines(25) and national laws in the participating countries. The study protocol has been approved by the Danish Committee on Health Research Ethics for the Capital Region of Denmark, the Danish Medicines Agency, Medical Research Ethics Committee Erasmus MC, and Ethics Committee of the Canton Bern. The trial was monitored by the regional Good Clinical Practice unit or by a local monitor unit. Management of data was approved according to national legislation. Patient insurances were in place either through the national health insurance or through specifically supplied local trial insurances at all trial sites according to the specific trial site and national regulations.

6.2 Protocol amendments
Substantial deviations from the protocol will be registered prior to implementation.

6.3 Declarations of interests
The TRAUMOX2 trial was initiated by a research group of medical doctors at the Department of Anaesthesia and Trauma Centre, University Hospital of Copenhagen, Rigshospitalet. It is funded by a grant (NNF20OC0063985) from the Novo Nordisk Foundation, a non-profit organisation, and by the Lundbeck Foundation as a personal grant to study coordinator Josefine Bækgaard. Investigator Felicia Dinesen has received funding from the Danish Air Ambulance and Rigshospitalets Forskningspuljer to cover salary. Further, sponsor Jacob Steinmetz has received funding from "Savværksejer Jeppe Juhl og Hustru Ovita Juhl Mindelegat", some of which was spent on salary to Dinesen. None of the foundations were involved in neither the study itself nor the decision to submit

the manuscript for publication. Jacob Steinmetz holds a position as clinical professor funded by Norwegian Air Ambulance Foundation. The investigators have no further conflicts of interest with any of the foundations.

6.4 Dissemination policy

The study results will be submitted to an appropriate peer-reviewed scientific journal. All authors must fulfil the criteria for authorship according to the ICMJE guidelines. Collaborators that do not meet the criteria for authorship will be listed as collaborators in the TRAUMOX2-study group and thereby be trackable via PubMed.

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Til forsøgspersonen

Information om deltagelse i et sundhedsvidenskabeligt forskningsprojekt med forsøgspersoner indlagt på hospitalet efter akut svær tilskadekomst

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

Vi vil spørge, om du vil deltage i et sundhedsvidenskabeligt forskningsprojekt, der foregår på det hospital i Danmark, du er blevet indlagt på.

Forsøget er startet allerede under den umiddelbare (akutte) behandling, da du ikke var i stand til at give samtykke ved skadestedet eller ankomst til TraumeCentret. En uafhængig læge har givet os samtykke til at starte forsøget på det tidspunkt, men nu spørger vi også om dit samtykke til deltagelse, selvom forsøget allerede er startet. Indtil du har givet dit eventuelle samtykke, har vi kun indsamlet oplysninger om din alder, skadesmekanisme og din transport til hospitalet.

Før du beslutter, om du vil deltage i forsøget, skal du fuldt ud forstå, hvad forsøget går ud på, og hvorfor vi gennemfører forsøget. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Du vil blive inviteret til en samtale om forsøget, hvor denne deltagerinformation vil blive uddybet, og hvor du kan stille de spørgsmål, du har om forsøget. Du er velkommen til at tage et familiemedlem, en ven eller en bekendt med til samtalen. Fra du er blevet informeret om forsøget har du op til 24 timers betænkningstid til at træffe en beslutning, om du fortsat vil deltage. Indtil du har informeret om din beslutning er du fortsat med i forsøget.

Hvis du beslutter dig for at deltage i forsøget, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til betænkningstid, før du beslutter, om du vil underskrive samtykkeerklæringen.

Det er frivilligt at deltage i forsøget. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for din videre behandling.

Formål med forsøget
Projektet har til formål at undersøge, hvorledes behandling med ekstra ilt (mere end de 21 %, der findes naturligt i vores indåndingsluft) umiddelbart efter tilskadekomst påvirker ens helbred efterfølgende.

Det er helt almindeligt at give ekstra ilt til akutte tilskadekomne. Dette gives for at undgå iltmangel, hvilket er en skadelig tilstand. Det er dog blevet påvist, at for meget ilt kan skade nogle slags patienter, eksempelvis patienter med blodprop i hjertet. På nuværende tidspunkt ved man ikke definitivt, om det samme kunne gøre sig gældende for patienter, der er kommet akut til skade. Det primære formål med dette projekt er at undersøge effekten af en mindre, men tilstrækkelig, iltdosis og sammenligne dette med en høj iltdosis, som i øjeblikket er standardbehandlingen.

Plan: Vi ønsker derfor at udføre et projekt, hvor forsøgspersoner, som er kommet akut til skade, ved lodtrækning vil få tildelt en af følgende to behandlinger i **de første 8 timer:**

A. En mindre, men tilstrækkelig, iltdosis

B. En høj iltdosis (standardbehandling)

Som forsøgsperson i forsøget vil du modtage behandling og overvågning som alle andre tilskadekomne patienter på hospitalet.

Plan for forsøget

Forsøget udføres af læger i et samarbejde mellem den præhospitale organisation (akutlægebil & akutlægehelikopter), anæstesiafdelingen (narkose), TraumeCentret, intensivafdelingen samt diverse afdelinger på hospitalet.

Vi ønsker at indsamle data på 1600 forsøgspersoner.

Udover din tilladelse til at indgå i forsøget, så vil vi anmode dig om lov til at tilgå din journal i op til 14 måneder efter din tilskadekomst. Vi vil bruge data fra journalen fra den aktuelle indlæggelse samt oplysninger om dit helbred i relation til din tilskadekomst. De involverede parter, der skal have adgang til at indhente journaloplysninger, er forskningsprojektpersonalet, Good Clinical Practice-enhederne i Danmark (i forbindelse med overvågning og kvalitetskontrol af kliniske forsøg) og Lægemiddelstyrelsen (i kraft af deres lovpligtige inspektion af kliniske forsøg). Der vil derfor i forsøget blive behandlet personoplysninger, og du orienteres hermed om, at både databeskyttelsesloven og databeskyttelsesforordningen overholdes.

Ydermere ønsker vi at høre dig, om vi må kontakte dig henholdsvis 6 og 12 måneder efter din tilskadekomst og foretage en kort, mundtlig undersøgelse af dit helbred. Det vil foregå telefonisk eller ved at besøge dig på din sengeafdeling, såfremt du fortsat er indlagt.

Hvem KAN deltage?

Du kan deltage, hvis du er ankommet direkte fra skadestedet til TraumeCentret efter tilskadekomst.

Hvem KAN IKKE deltage?

Du kan ikke deltage, hvis du opfylder et af nedenstående kriterier:

- Du er under 18 år gammel
- Du har en væsentlig røgforgiftning
- Hvis du har haft hjertestop efter tilskadekomsten
- Hvis det viser sig, at du har små eller ingen skader, der muliggør, at du udskrives inden for 24 timer efter indlæggelse

Det er den klinisk ansvarlige læge, der afgør om deltagelse i forsøget er mulig.

Biologisk materiale

Vi vil i en særskilt deltagerinformation og samtykkeerklæring spørge dig, om du vil donere biologisk ekstra materiale i form af ca. 20 ml blod ved indlæggelsen samt ca. 20 ml blod dagen efter din indlæggelse, uden direkte relation til dette forskningsprojekt, til en biobank med henblik på fremtidig forskning.

For forsøgspersoner indlagt på Odense Universitetshospital og Århus Universitetshospital vil der ikke blive udtaget dette ekstra biologiske materiale.

Nytte ved forsøget

Dette forskningsprojekt har til formål at øge forståelsen af, hvordan forskellige doseringer af iltbehandling påvirker kroppen efter en tilskadekomst. Vores hypotese er, at den mindre, men tilstrækkelige, iltdosis vil kunne komme den enkelte patient til gavn i form af færre lungekomplikationer. Yderligere har vi en forventning om, at resultaterne på længere sigt kan bidrage til en bedre forståelse for iltbehandling til akutte tilskadekomne.

Bivirkninger, risici, komplikationer og ulemper

På nuværende tidspunkt giver man højdosis ilt til akutte tilskadekomne patienter som standardbehandling, velvidende at det i for høje koncentrationer kan give bivirkninger i form af lungeproblemer samt let nedsat puls. Vi tror derfor, at man ved at reducere iltmængden kunne mindske disse bivirkninger.

På den anden side er der en risiko for at få for lidt ilt, når ilttilførslen nedsættes. Vi vil dog hele tiden sikre os, at dette ikke sker ved at måle dit iltindhold i blodet; dette gør vi ved hjælp af en iltmåler på fingeren samt udtagelse af blodprøver. Yderligere kan der være eventuelle uforudsete gener eller belastninger ved at deltage i forsøget, som vi ikke kender til. Dog har ilt har været anvendt i over 100 år som lægemiddel. Som tidligere nævnt bliver du behandlet helt på lige fod med andre tilskadekomne med hensyn til den øvrige behandling og du vil blive meget tæt overvåget.

Udelukkelse fra og afbrydelse af forsøg

Du vil blive udelukket fra forsøget, såfremt du ikke giver samtykke til forsøget eller hvis du opfylder et af udelukkelseskriterierne angivet ovenfor.

Oplysninger om økonomiske forhold

Forsøget er økonomisk støttet af Novo Nordisk Fonden over en 4-årig periode, hvorfra der er bevilliget 6.326.084 kr. Pengene går til studiets administrative omkostninger for de involverede parter. Herudover er studiet også støttet af Lundbeckfonden gennem et personligt stipendie på 350.000 kr. til studiekoordinator Josefine Bækgaard. Dette stipendie vil delvist bidrage til aflønning af Bækgaard samt uforudsete udgifter under afviklingen af studiet.

Forskningsprojektet er igangsat af en forskningsgruppe bestående af læger på Afdeling for Bedøvelse, Operation og TraumeCenter, HovedOrtoCentret, Rigshospitalet. Iltbehandling er allerede en del af standardbehandling til patienter, der kommer akut til skade. Novo Nordisk Fonden eller Lundbeckfonden

har ingen økonomisk interesse i ilt og har ikke haft nogen indflydelse på forsøgets design, udførelse samt kommende data- og publikationsproces.

Adgang til forsøgsresultater

Forskningsprojektets resultater vil blive offentliggjort i et internationalt anerkendt tidsskrift så snart data er analyseret. Vi forventer, at resultaterne vil være offentligt tilgængelige i løbet af 2024. Når resultaterne er analyseret og publiceret, så vil vi henvise til disse via vores hjemmeside, som du kan tilgå via dette internetlink https://www.traumox2.org/.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i forsøget, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Vi beder dig også om at læse det vedlagte materiale "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt".

Hvis du vil vide mere om forsøget, er du meget velkommen til at kontakte undertegnede:

Tobias Arleth
Læge, ph.d.-studerende
Afdeling for Bedøvelse, Operation og TraumeCenter
HovedOrtoCentret, Rigshospitalet
Inge Lehmanns Vej 6, opgang 6, 1. sal, afsnit 6011
2100 København Ø
Tlf.: +45 35 45 95 02
E-mail: tobias.arleth@regionh.dk

Med venlig hilsen

Tobias Arleth, læge, ph.d.-studerende, koordinerende forsøgsansvarlig
Jacob Steinmetz, professor, overlæge, ph.d., sponsor og initiativtager til forsøget

Informeret samtykke
(forsøgsperson)
til deltagelse i et sundhedsvidenskabeligt forskningsprojekt

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

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til at deltage i forskningsprojektet. Jeg har fået en kopi af den skriftlige information om projektet til eget brug. Jeg er også blevet tilbudt en kopi af dette samtykkeark til eget brug, hvis jeg ønsker sådan en.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?

Ja _____ (sæt X) Nej _____ (sæt X)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift: _____

Dato og underskrift fra patienten kan også laves i REDCap og er koblet specifikt til patientens forløb.

Videnskabetisk Komité journal-nr.: H-21018062
EudraCT nummer: 2021-000556-19

Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt

Som deltager i et sundhedsvidenskabeligt forskningsprojekt skal du vide, at:

- din deltagelse i forskningsprojektet er helt frivillig og kun kan ske efter, at du har fået både skriftlig og mundtlig information om forskningsprojektet og underskrevet samtykkeerklæringen.
- du til enhver tid mundtligt, skriftligt eller ved anden klar tilkendegivelse kan trække dit samtykke til deltagelse tilbage og udtræde af forskningsprojektet. Såfremt du trækker dit samtykke tilbage påvirker dette ikke din ret til nuværende eller fremtidig behandling eller andre rettigheder, som du måtte have.
- du har ret til at tage et familiemedlem, en ven eller en bekendt med til informationssamtalen.
- du har ret til betænkningstid, før du underskriver samtykkeerklæringen.
- oplysninger om dine helbredsforhold, øvrige rent private forhold og andre fortrolige oplysninger om dig, som fremkommer i forbindelse med forskningsprojektet, er omfattet af tavshedspligt.
- behandling af oplysninger om dig, herunder oplysninger i dine blodprøver og væv, sker efter reglerne i databeskyttelsesforordningen, databeskyttelsesloven samt sundhedsloven. Den dataansvarlige i forsøget skal orientere dig nærmere om dine rettigheder efter databeskyttelsesreglerne.
- der er mulighed for at få aktindsigt i forsøgsprotokoller efter offentlighedslovens bestemmelser. Det vil sige, at du kan få adgang til at se alle papirer vedrørende forsøgets tilrettelæggelse, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre.
- der er mulighed for at klage og få erstatning efter reglerne i lov om klage- og erstatningsadgang inden for sundhedsvæsenet. Hvis der under forsøget skulle opstå en skade kan du henvende dig til Patienterstatningen, se nærmere på www.patienterstatningen.dk

De Videnskabsetiske Komiteer for Region Hovedstaden (6 komiteer)
Tlf.: +45 38 66 63 95
E-mail: vek@regionh.dk
Hjemmeside:
https://www.regionh.dk/til-fagfolk/Forskning-og-innovation/Kliniske-test-og-forsoeg/Sider/De-Videnskabsetiske-Komitéer.aspx

De Videnskabsetiske Komiteer for Region Syddanmark (2 komiteer)
Tlf.: + 45 76 63 82 21
E-mail: komite@rsyd.dk
Hjemmeside:
https://komite.regionsyddanmark.dk/wm258128

Den Videnskabsetiske Komité for Region Nordjylland Tlf.: +45 97 64 84 40
E-mail: vek@rn.dk
Hjemmeside:
http://www.rn.dk/vek

Den Videnskabsetiske Komité for Region Sjælland
Tlf.: +45 93 56 60 00
E-mail: RVK-sjaelland@regionsjaelland.dk
Hjemmeside:
https://www.regionsjaelland.dk/sundhed/forskning/forfagfolk/videnskabsetisk-komite/Sider/default.aspx

De Videnskabsetiske Komiteer for Region Midtjylland (2 komiteer)
Tlf.: +45 78 41 01 83 / +45 78 41 01 82 / +45 78 41 01 81
E-mail: komite@rm.dk
Hjemmeside:
http://www.komite.rm.dk

National Videnskabsetisk Komité
Tlf.: +45 72 21 68 55
E-mail: kontakt@nvk.dk
Hjemmeside: http://www.nvk.dk

Dette tillæg er udarbejdet af det videnskabsetiske komitésystem og kan vedhæftes den skriftlige information om det sundhedsvidenskabelige forskningsprojekt. Spørgsmål til et konkret projekt skal rettes til projektets forsøgsansvarlige. Generelle spørgsmål til forsøgspersoners rettigheder kan rettes til den komité, som har godkendt projektet.

Revideret 21. september 2019

To the study participant

Information about participation in a research study with study participants admitted to the hospital after acute severe injury

Study title: **Comparing Restrictive vs Liberal Oxygen Strategies for Trauma Patients: The TRAUMOX2 Trial**

We would like to ask if you would like to participate in a research study at the hospital in Denmark to which you have been admitted.

The study already started during your initial (acute) treatment, as you were not able give consent at the scene of the injury or arrival at the Trauma Centre. At that time an independent physician gave consent to start the study, but now we are also asking for your consent to participate, even though the study has already started. Until you have given your potential consent, we have only collected information about your age, mechanism of injury, and transportation to the hospital.

Before you decide whether you want to participate in the study, you must fully understand what the study is about and why we are conducting the study. Therefore, we would like you to read this study participant information carefully. You will be invited for a conversation on the study where this study participant information will be explained in detail and where you may ask any questions you may have about the study. Please feel free to bring a family member, friend or acquaintance to the conversation. Once you have been informed about the study, you have up to 24 hours to consider whether you want to continue participating. Until you have informed us of your decision, you will continue participating in the study.

If you decide to participate in the study, we will ask you to sign a consent form. You have the right to a reflection period before deciding whether you want to sign the consent form.

Participation in the study is voluntary. You can withdraw your consent at any time and without giving a reason. It will not have any consequences for your further treatment.

Purpose of the study
The study aims to investigate the impact of treatment with extra oxygen (more than the 21% found naturally in our inhaled air) immediately after an injury.

It is quite common to give extra oxygen to acutely injured people. This is done to avoid oxygen deficiency, which is a known harmful condition. However, it has been shown that too much oxygen can harm some types of patients, such as patients with blood clots in the heart. At present, it is not definitively known whether the same could apply to patients who have been acutely injured. The primary purpose of this study is to compare a smaller, but adequate dose of oxygen with a high dose of oxygen, which is currently the standard treatment.

Therefore, we want to carry out a study in which study participants, who have been acutely injured, by randomisation will be given one of the following two treatments for **the first 8 hours:**

A. A smaller, but adequate dose of oxygen

B. A high oxygen dose (standard treatment)

All other treatment will not differ to patients not participating in the study.

Plan

The study is conducted by physicians in a collaboration between the pre-hospital organisation (physician staffed emergency ambulances & helicopters), the anaesthesia department, the trauma centre, the intensive care unit, and various departments at the hospital.

We want to collect data on 1600 study participants.

In addition to your permission to take part in the study, we will ask you for permission to access your medical record for up to 14 months after your injury. We will use data from the medical record from the current hospitalisation and information about your health impacted by your injury. The parties involved who must have access to obtain medical record information are the research study staff, the Good Clinical Practice units in Denmark (in connection with monitoring and quality control of clinical trials) and the Danish Medicines Agency (under their statutory inspection of clinical trials). Therefore, personal data will be processed in the study, and you are hereby informed that we comply with both the Data Protection Act and the Data Protection Ordinance.

Furthermore, we would like to ask for your permission to contact you 6 and 12 months after your injury, respectively, for a brief talk about your health. This will be done by telephone or by visiting you in your ward if you are still hospitalised.

Who CAN participate?

You can participate if you have arrived directly from the scene of the accident to the Trauma Centre after the injury.

Who CAN NOT participate?

You can not participate if you meet one of the following criteria:

- You are under 18 years old
- You have a significant smoke poisoning
- If you have had a cardiac arrest after the injury
- If it turns out that you have few or no injuries that allows you to be discharged within 24 hours after admission

The clinically responsible physician decides whether participation in the study is possible.

Biological material

In a separate study participant information and consent form, please indicate if you agree to let us use your blood samples for future research. If yes, we will draw 20 ml of blood at admission and approximately 20 ml

of blood the day after your admission, with no direct relation to this research study, but for a biobank for future research.

This additional biological material will not be extracted for study participants admitted to Odense University Hospital and Aarhus University Hospital.

The benefits of the study

This research study aims to increase the understanding of how different dosages of oxygen therapy affect the body after an injury. We hypothesise that the smaller, but adequate dose of oxygen could benefit the individual patient by reducing the risk of lung complications. Furthermore, we expect that the results in the long term can contribute to a better understanding of oxygen treatment for acutely injured patients in general.

Side effects, risks, complications and disadvantages

At present, high dose oxygen is given to acutely injured patients as the standard treatment, knowing that in too high concentrations, it can cause side effects by causing lung problems as well as slightly reduced heart rate. Therefore, we think that reducing the amount of oxygen could reduce these side effects.

On the other hand, there is a risk of receiving too little oxygen when reducing oxygen delivery. However, to avoid this we will monitor the concentration of oxygen in your blood very carefully with the help of a pulse oximeter on the finger as well as taking blood samples. Finally, there may be any unforeseen inconveniences or strains from participating in the study we are unaware of. However, oxygen has been used for more than 100 years as a medicine.

Please rest assured that you will be treated equally to other trauma patients concerning the rest of the treatment, and you will be very closely monitored through the length of your hospital stay.

Exclusion from and interruption of studys

You will be excluded from the study if you do not consent to the study or if you meet one of the exclusion criteria listed above.

Information on financial matters

The Novo Nordisk Foundation financially supports the study over four years, from which DKK 6,326,084 has been granted. The money goes to the administrative costs of the study for the parties involved. In addition, the study is also supported by the Lundbeck Foundation through a personal scholarship of DKK 350,000 to study coordinator Josefine Bækgaard. This scholarship will partly contribute to the remuneration of Bækgaard as well as unforeseen expenses during the completion of the study.

The research study was initiated by a research group consisting of physicians at the Department of Anaesthesia and Trauma Centre, Centre of Head and Orthopaedics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. Oxygen therapy is already part of standard treatment for acutely injured patients. The Novo Nordisk Foundation or the Lundbeck Foundation have no financial interest in oxygen and have not influenced the study's design, execution and future data and publication process.

Access to study results

The research study results will be published in an internationally recognised journal as soon as the data is analysed. We expect the results to be publicly available in 2024. Once the results have been analysed and published, we will refer to these via our website, which you can access via this internet link https://www.traumox2.org/.

We hope that you have gained sufficient insight into what it means to participate in the study and that you feel equipped to decide on your possible participation with this information.

If you want to know more about the study, you are very welcome to contact:

Tobias Arleth
Medical doctor, PhD student
Department of Anaesthesia and Trauma Centre
Centre of Head and Orthopaedics, Rigshospitalet
Inge Lehmanns Vej 6, entrance 6, 1st floor, section 6011
2100 Copenhagen Ø
Tel. : +45 35 45 95 02
E-mail: tobias.arleth@regionh.dk

Yours sincerely

Tobias Arleth, medical doctor, PhD student, coordinating investigator
Jacob Steinmetz, professor, consultant, PhD, study leader and initiator of the study

Informed consent
(study participant)
for participation in a research study

Title of the research study: Comparing Restrictive vs Liberal Oxygen Strategies for Trauma Patients: The TRAUMOX2 Trial

Statement from the study participant:

I have received written and oral information, and I know enough about the purpose, method, advantages and disadvantages of saying yes to participating.

I know that participating is voluntary and that I can always withdraw my consent without losing my current or future rights to treatment.

I consent to participate in the research study. I have received a copy of the written information about the study for my own use. I have also been offered a copy of this consent form for my own use.

Name of study participant: _____

Date:_____ Signature: _____

Do you want to be informed about the results of the study alongside any potential consequences for you?

Yes _____ (mark X) No _____ (mark X)

Statement from the person providing the information:

I declare that the study participant has received oral and written information about the study.

In my opinion, sufficient information has been provided to enable a decision on participation in the study.

The name of the person who provided the information:

Date: _____ Signature: _____

The date and signature from the study participant can also be made in REDCap and are linked specifically to the study participant's course.

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