PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing Restrictive vs. Liberal Oxygen Strategies for Trauma Patients - The TRAUMOX2 Trial: Protocol for a Randomised Clinical Trial
AUTHORS	Baekgaard, Josefine; Arleth, Tobias; Siersma, Volkert; Hinkelbein, Jochen; Yuecetepe, Sirin; Klimek, M; van Vledder, Mark; Van Lieshout, Esther M.M.; Mikkelsen, Søren; Zwisler, Stine; Andersen, M. S.; Fenger-Eriksen, Christian; Isbye, Dan; Rasmussen, Lars; Steinmetz, Jacob

VERSION 1 – REVIEW

REVIEWER	Peters, Mark Great Ormond Street Hospital For Children NHS Trust, Paediatric Intensive Care Unit
REVIEW RETURNED	08-Jun-2022

GENERAL COMMENTS	Very much needed study - look forward to the results. Minor points - please present the FiO2 (fraction of inspired oxygen) as a fraction e.g. 0.8 not as a percentage. There a a few example where this has slipped through. Please clarity if the target for the intervention is the peripheral oxygen saturation estimated by pulse oximetry (SpO2) or the directly measured arterial oxyhaemoglobin saturation(SaO2). Currently the wording is incorrect and could mean either: "arterial oxyhaemoglobin saturation (SpO2) target of 94%" For clarity I would suggest the sentence in both the abstract and the text: The primary outcome is the incidence of 30-day mortality and/or major respiratory complications (pneumonia and/or ARDS) (composite outcome). is reworded as The primary outcome is a composite of 30-day mortality and/or development of major respiratory complications (pneumonia and/or ARDS). Under "definitions" please expand the abbreviation AIS The text following the Ethics and Dissemination heading includes 4 (the last 4 before Protocol changes) paragraphs that do not appear to belong here. I suspect most of these could be deleted or greatly reduced and should appear in the description of the intervention earlier in the methods

	Discussion: "time gap may be much larger" suggest "time gap may be much longer"

REVIEWER	Douin, David University of Colorado Denver School of Medicine
REVIEW RETURNED	09-Jun-2022

GENERAL COMMENTS	The authors report a protocol for the ongoing TRAUMOX2 trial, comparing restrictive versus liberal oxygen strategies for major trauma patients. While the benefits of avoiding hyperoxemia in critically ill patients are well-established, an important knowledge gap exists in trauma patients. The authors' protocol is detailed, well written, and thoroughly explains their expected methods and reporting of results. I have only minor comments: 1) Please elaborate on and support your choice of 94% as the lower limit for SpO2 in the restrictive group. Why not target an SpO2 of at least 92%, or even 90%? 2) You mention pneumonia is diagnosed via CDC criteria (including citation), however, you do not elaborate further. Pneumonia tends to be a heterogeneous disease with a variety of clinical manifestations and severities. Since pneumonia is a major component of your primary composite endpoint, it is important to be clear how you will diagnose this condition. Please include your criteria for diagnosis of pneumonia on page 12, line 35. 3) Please also include a short description of the Berlin Criteria for ARDS, as you have done for TBI.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Prof. Mark Peters, Great Ormond Street Hospital For Children NHS Trust, University College London
Comments to the Author: Very much needed study - look forward to the results.

Minor points - please present the FiO2 (fraction of inspired oxygen) as a fraction e.g. 0.8 not as a percentage. There are a few examples where this has slipped through.
Thank you, this has been adjusted.

Please clarity if the target for the intervention is the peripheral oxygen saturation estimated by pulse oximetry (SpO2) or the directly measured arterial oxyhaemoglobin saturation(SaO2).
Currently the wording is incorrect and could mean either: "arterial oxyhaemoglobin saturation (SpO2) target of 94%"
Thank you, this has been clarified on page 6. The target is indeed the arterial oxyhaemoglobin saturation (SaO2) measured by pulse oximetry (SpO2).

For clarity I would suggest the sentence in both the abstract and the text:
The primary outcome is the incidence of 30-day mortality and/or major respiratory complications (pneumonia and/or ARDS) (composite outcome).
is reworded as

The primary outcome is a composite of 30-day mortality and/or development of major respiratory complications (pneumonia and/or ARDS).
Thank you for this suggestion. The sentence has been changed accordingly.

Under "definitions" please expand the abbreviation AIS
Thank you for pointing this out, it has been expanded.

The text following the Ethics and Dissemination heading includes 4 (the last 4 before Protocol changes) paragraphs that do not appear to belong here. I suspect most of these could be deleted or greatly reduced and should appear in the description of the intervention earlier in the methods
Thank you, these were meant as further explanations on the ethics, but have now been deleted as per your suggestion.

Discussion:
"time gap may be much larger" suggest "time gap may be much longer"
Thank you, this has been changed.

Reviewer: 2
Dr. David Douin, University of Colorado Denver School of Medicine
Comments to the Author:
The authors report a protocol for the ongoing TRAUMOX2 trial, comparing restrictive versus liberal oxygen strategies for major trauma patients. While the benefits of avoiding hyperoxemia in critically ill patients are well-established, an important knowledge gap exists in trauma patients. The authors' protocol is detailed, well written, and thoroughly explains their expected methods and reporting of results. I have only minor comments:

1) Please elaborate on and support your choice of 94% as the lower limit for SpO2 in the restrictive group. Why not target an SpO2 of at least 92%, or even 90%?
Thank you for this question. The target of 94% has been carefully chosen and is based on previous studies as explained in the discussion, page 13, 2nd paragraph.
“A large randomised study on patients with myocardial infarction showed that targeting an SpO2 of 94% resulted in a decrease in myocardial injury and myocardial infarct size.[37] Another study has shown a dramatic increase in the occurrence of hyperoxaemia when SpO2 was above 95%,[38] and for those reasons, we have chosen SpO2 94% to be the target in the restrictive group.”
37 Stub Dion, Smith Karen, Bernard Stephen, et al. Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction. Circulation 2015;131:2143–50. doi:10.1161/CIRCULATIONAHA.114.014494
38 Durlinger EMJ, Spoelstra-de Man AME, Smit B, et al. Hyperoxia: At what level of SpO2 is a patient safe? A study in mechanically ventilated ICU patients. J Crit Care 2017;39:199–204. doi:10.1016/j.jcrc.2017.02.031

Furthermore, as mentioned in the discussion as well, the British Thoracic Society recommends initial management with high-concentration oxygen therapy and a target SpO2 of 94–98% for both hypoxaemic patients and patients ‘at risk of hypoxaemia’. We have therefore been inspired by their lower limit for our trial.
O’Driscoll BR, Howard LS, Earis J, et al. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 2017;72:ii1–90. doi:10.1136/thoraxjnl-2016-209729
In addition the consensus statement of the Seattle International Traumatic Brain Injury Conference recommends that the initial treatment of TBI patients should be an SpO2>94 (Hawryluk et al. Intensive care Med 2019; 45:1783–1794).
Finally, in the pilot trial, TRAUMOX1 maintenance of normoxaemia post trauma appeared feasible and there were few episodes of hypoxaemia using the same target.

Baekgaard JS, Isbye D, Ottosen CI, et al. Restrictive vs liberal oxygen for trauma patients-the TRAUMOX1 pilot randomised clinical trial. Acta Anaesthesiol Scand;63:947–55. doi:10.1111/aas.13362

2) You mention pneumonia is diagnosed via CDC criteria (including citation), however, you do not elaborate further. Pneumonia tends to be a heterogeneous disease with a variety of clinical manifestations and severities. Since pneumonia is a major component of your primary composite endpoint, it is important to be clear how you will diagnose this condition. Please include your criteria for diagnosis of pneumonia on page 12, line 35.
3) Please also include a short description of the Berlin Criteria for ARDS, as you have done for TBI.

Question 2 and 3:
Thank you for this suggestion. The details of the criteria for the diagnosis of pneumonia and ARDS are outlined in figure 2.
If the editor agrees, we are happy to include it in the text as well.

Reviewer: 1
Competing interests of Reviewer: Chief Investigator of NIHR HTA funded Oxy-PICU-PICU trial of Conservative vs Liberal Oxygenation Strategies in Critically Ill Children

Reviewer: 2
Competing interests of Reviewer: I am a contributing member of a similar trial, the SAVE-O2 clinical trial (NCT04534959).

VERSION 2 – REVIEW

REVIEWER	Douin, David University of Colorado Denver School of Medicine
REVIEW RETURNED	09-Sep-2022

GENERAL COMMENTS	Thank you for responding to all comments. No additional comments at this time