TITLE:

A feasibility randomised controlled trial of targeted oxygen therapy in mechanically ventilated critically ill patients

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ABSTRACT

Background: Despite oxygen being the commonest drug administered to critically ill patients we do not know which oxygen saturation (SpO_2) target results in optimal survival outcomes in those receiving mechanical ventilation. We therefore conducted a feasibility randomised controlled trial in the United Kingdom (UK) to assess whether it would be possible to host a larger national multi-centre trial to evaluate oxygenation targets in mechanically ventilated patients.

Methods: We set out to recruit 60 participants across two sites into a trial in which they were randomised to receive conservative oxygenation (SpO_2 88-92%) or usual care (control – SpO_2 ≥96%). The primary outcome was feasibility; factors related to safety and clinical outcomes were also assessed.

Results: A total of 34 patients were recruited into the study until it was stopped due to time constraints. A number of key barriers to success were identified during the course of the study. The conservative oxygenation intervention was feasible and appeared to be safe in this small patient cohort and it achieved wide separation of the median time-weighted average (IQR) SpO_2 at 91% (90-92%) in conservative oxygenation group versus 97% (96-97%) in control group.

Conclusion: Whilst conservative oxygenation was a feasible and safe intervention which achieved clear group separation in oxygenation levels, the model used in this trial will require alterations to improve future participant recruitment rates in the UK.

INTRODUCTION

Oxygen is one of the commonest drugs used in the management of acutely unwell patients with respiratory failure requiring mechanical ventilation on an intensive care unit (ICU). Despite this, there is little available evidence or guidance on what level of arterial oxygenation that favours improved survival. It has been proposed that reducing arterial oxygenation targets (termed 'permissive hypoxaemia') may not only be safe but might also improve clinical outcomes[1]. A number of studies have attempted to explore the relationship between oxygenation and survival in critically ill patients by analysing retrospective datasets.[2–4] The results have been varied and the conclusions must be interpreted with care as it is difficult to avoid confounding by treatment intention (i.e. the more unwell a patient is the greater likelihood of over-oxygenation) using this methodological approach. A recent study of hyperoxaemia in patients admitted to ICU in England used novel methods to reduce confounding and concluded that there was an association between hyperoxaemia and mortality, but did not explore the relationship between hypoxaemia and survival.[5] Three recently published, moderate sized randomised controlled trials evaluating conservative oxygen therapy protocols have shown conflicting results in the critically ill. The first, a single-centre study (n=434) comparing an oxygen saturation (SpO_2) target range of 94-98% to usual therapy was stopped early, reporting a substantial reduction in morality in the intervention group.[6] The second, a multi-centre study (n=1000) comparing an SpO_2 target range of 91-96% to usual care, showed no difference in ventilator-days or survival between oxygenation groups.[7] The third, a multi-centre study of patients with acute respiratory distress syndrome (ARDS) (n=205, comparing an SpO_2 target range of 88-92% to ≥96%) was also stopped early and showed no difference in 28 day survival.[8] The situation is further complicated by the fact that each study recruited different critically ill populations (in terms of severity of illness and diagnosis) and implemented different intervention and control group oxygenation targets. It is therefore impossible to draw any clear conclusion about oxygenation and survival in mechanically ventilated patients based on the current published

evidence except to say that there is strong historical evidence of increased mortality for critical care patients with very low oxygen saturation levels (SpO_2 <85%) and there is moderate evidence of harm from marked hyperoxaemia with an arterial partial pressure of oxygen (PaO_2) >200 mmHg or 26 kPa, equivalent to an SpO_2 of 99%-100%.

We therefore set out to conduct a randomised controlled trial to assess the feasibility of recruiting mechanically ventilated patients admitted to ICUs in England into a study evaluating a conservative oxygenation intervention. The purpose of the study was to determine criteria that could be used in a subsequent large trial to evaluate the efficacy and cost effectiveness of the intervention.

METHODS

Trial design

The Targeted OXYgen therapY in Critical illness (TOXYC) trial was designed according to the standard protocol items: recommendations for interventional trial (SPIRIT) statements.[9] Its purpose was to determine the feasibility of conducting a randomised controlled trial of a lower than normal (conservative) SpO_2 target in adult critically ill patients requiring mechanical ventilation in a National Health Service (NHS) setting. The study was approved by the London Harrow Research Ethics Committee (reference 17/LO/1334) along with approval from the Health Research Authority. The trial protocol and statistical analysis plan were published prior to completion of participant recruitment.[10] The aim was to recruit a total of 60 patients across two sites in England (the Royal Free Hospital, London and Southampton General Hospital) in 15 months; recruitment commenced in January 2018.

Patients

Eligible patients were mechanically ventilated adults (18 years of age or older) within 24 hours of an unplanned admission to ICU, who had a diagnosis of respiratory failure and where it was thought mechanical ventilation was expected to be required for 72 hours or more. Exclusions to enrolment included: admission following surgery (elective or unplanned), patients expected to die within 24 hours of admission to ICU, pregnant women, admission post-cardiac arrest, patients with chronic lung disease known (or highly suspected) to have baseline SpO_2 in the range of the intervention arm (88-92%), admission post-trauma (including traumatic brain injury), known sickle cell trait or disease, ongoing significant haemorrhage or profound anaemia, severe peripheral vascular disease, severe pulmonary hypertension, other medical conditions where mild hypoxaemia would be contraindicated, and participation in another interventional clinical trial. Agreement to participate in the study was sought from the patient (if they were deemed to have capacity), a personal consultee, or professional consultee as appropriate.[10] All patient consent and consultee agreement procedures adhered to the Mental Capacity Act (2005).

Randomisation and treatment

Patients were randomly assigned on a 1:1 basis (www.sealedenvelope.com) into either the conservative or control group, stratified by study site, using random permuted blocks of different sizes. In the conservative oxygen therapy group, the fractional inspired oxygen concentration (F_IO_2) was titrated to achieve an SpO_2 of 88%-92%; guidance was provided to bedside staff but the process was not protocolised. In the control group, F_IO_2 was adjusted to maintain an SpO_2 at or above 96%. The study intervention was continued until extubation, formation of tracheostomy, transfer to another ICU or death. Due to the nature of the intervention, neither the research nor the clinical teams were blinded to participant group allocation.

Participants were reviewed by the research team on a daily basis in order to assess compliance with the SpO_2 criteria they were allocated to. Where a participant was briefly transferred out of ICU (e.g. investigation, or imaging) the trial was paused until they returned to ICU. Aside from the designated SpO_2 targets, all other aspects of care remained the same between the intervention and control cohorts. Regular arterial blood gases were taken during the trial, according to local clinical guidelines. Treating clinicians were able to withdraw participants from the study at any point if were there any medical concerns.

Protocol major amendments

During the course of the trial, it was necessary to amend the study protocol; the major amendments are summarised below:

January 2018 (NOSA001): An addition to the inclusion criteria to allow patients intubated whilst on ICU to be considered for enrolment within 24 hours of intubation. In the inclusion criteria, the expected duration of a potential participant remaining intubated was reduced from >72 hours to >24 hours.

September 2018 (NOSA002): An additional level of agreement to participate in the study was introduced for patients who were deemed to lack the capacity to consent prior their current acute illness.

February 2019 (NOSA003): The removal of the requirement to maintain an SpO_2 of ≥96% for the participants allocated to the control group; i.e. patients allocated to the control group had their oxygenation managed purely by the clinical team, without any restrictions. This was necessary as clinicians claimed that the ≥96% target did not reflect usual practice.

Outcome measures

The primary outcome of the study was feasibility; this was defined as the ability to recruit patients and the rate of participant withdrawal from the study. Support for the trial from clinicians and the reasons for withdrawal from the study were also assessed. Feasibility of

recruitment was evaluated by monitoring patient screening and their subsequent agreement to participate, along with any withdrawal of consent during or after the study. As part of the feasibility assessment, adherence to the oxygenation targeting component of the study protocol was assessed by monitoring hourly SpO_2 and any logged protocol deviations.

A number of secondary outcome measures were evaluated in order to determine relevant endpoints for future trials and to explore potential biological mechanisms. Clinical secondary outcomes included ICU and hospital length of stay, survival at ICU discharge, 30 and 90 days, and pre-defined adverse events, and change in the sequential organ failure assessment (SOFA) score over time. Key physiological measures were also recorded during the intervention period. Blood samples were taken at baseline and on days 2, 3, 5 and 10 after recruitment to measure an array of selected of biomarkers of oxidative stress (not reported here).

Statistical analysis

As the primary outcome measure of this trial was feasibility, no sample size calculation was performed. [11] In view of a predicted mortality of approximately 30% in the study cohort we chose to set our sample size on the higher end of what is usually considered to be acceptable for a feasibility study. Data were collected from bedside charts and entered into an electronic clinical record form (eCRF). Data analysis was conducted blinded to specific group allocation. Primary and secondary outcome measures were presented using summary statistics. Missing data, non-compliers and withdrawals were analysed to determine if was bias seemed likely. Daily time-weighted mean values of F_IO_2, SpO_2, PaO_2 and arterial partial pressure of carbon dioxide ($PaCO_2$) were calculated as an area under the curve using the area of trapezoids by multiplying the mean of the measured individual values by the duration of the interval, divided by the complete time of observation, then finding the sum of all values per participant in a 24 hour period. Similarly, for treatment time-weighted means the sum of all values was calculated for the total time on treatment (between 1 and 21 days). For each

patient, the proportion of time spent within the randomisation determined SpO_2 limits were calculated and summarised by treatment arm. Adverse events were tabulated and grouped according to seriousness, severity and causality.

RESULTS

The two sites recruited a total of 34 participants between February 2018 and October 2019. Recruitment of patients was terminated after the 34th patient as the trial had reached the end of its extended recruitment window.

Baseline and randomisation

Primary respiratory diagnosis and underlying comorbidities of participants are shown in Tables 1 and 2 respectively; 22 (64.7%) participants were male and the median age was 66 years (IQR 58 – 74). Key baseline respiratory measures are displayed in Table 3. 27 (79.4%) participants were on a mandatory mode of ventilation at the start of the intervention, 4 (11.8%) on a spontaneous mode and 4 (11.8%) on a mixed mode. Randomisation was balanced between the two treatment groups (17:17) and was also balanced at each site (10:10 at site one and 7:7 at site two). A summary of missing data is shown in the online supplementary information; no evidence of bias was detected.

Feasibility

The 34 participants were recruited over 622 days, an average rate of 20 participants per year or 1.7 per month. There were two withdrawals of consent from the study by Personal Consultees. Four participants were withdrawn from the study by the clinical team; reasons for this were i) development of a new stroke (intervention group); ii) concerns over excessively high F_IO_2 in a patient with bronchiectasis on a new CT scan (control group); iii) development of ischaemic colitis (intervention group); and iv) concerns over high F_IO_2 to

maintain the SpO_2 target (control group). A number of factors were identified that may have contributed to the low recruitment rate observed in this study:

- Method of obtaining consent from participants / agreement from consultees
- Control group SpO_2 parameters.
- Low number of recruitment centres
- Narrow inclusion criteria.

Intervention

The overall median (IQR) duration of intervention was 6 (3-10) days. The reason for the intervention being terminated in each participant (either within protocol or for other reasons) are summarised in Table 4.

Protocol adherence

Figure e2 in the online supplementary information shows the daily time-weighted mean values for SpO_2 according to randomisation group. Of the 17 participants randomised to the conservative oxygenation group, 73.1% of daily time-weighted mean values were between 88-92% SpO_2. Of the 17 participants randomised to usual care, 75.2% of daily time-weighted mean values were between 96 to 100% SpO_2.

Oxygenation measures

The median (IQR) time-weighted mean SpO_2 for participants in the conservative oxygen therapy group was 91 (90-92)% and for those in the control group it was 97 (96-97)% (Table 5). The daily time-weighted mean values for FIO_2, SpO_2, PaO_2 and $PaCO_2$ are shown in the online supplementary data (figures e1-e4 respectively).

Adverse events

There was a total of 75 adverse events reported in 24 participants; the details are summarised in the online supplementary information (Table e2). 37 of these adverse events were in the conservative oxygenation group and 38 in the control group. The adverse events appeared well balanced between the two groups in terms of severity, causality and expectedness. There was a total of 23 serious adverse events; 10 in the conservative oxygenation group and 13 in the control group. There were 5 deaths in the conservative oxygenation group and 4 in the control group. There appeared to be marginally more respiratory and cardiovascular adverse events in the conservative oxygenation than the control group (65% vs. 53%, and 71% vs. 53% respectively).

Clinical secondary outcomes

Table 6 displays the key clinical secondary outcome measures by randomisation group. There was a trend towards higher survival and shorter ICU and hospital length of stay in the control group. No statistical analyses were performed as the trial was not powered to detect a difference in these secondary measures.

DISCUSSION

Whilst a number of moderate sized RCTs have set out to address the issue of determining the optimal oxygenation targets in critically ill patients, none of them have been conducted in the setting of the UK NHS, and to date, no clear answer has emerged. For these reasons, we undertook a study to assess the feasibility of conducting a trial in which mechanically ventilated NHS patients were enrolled and randomised to assess a conservative approach to oxygenation (SpO_2 88-92%). The primary outcome of this trial was an assessment of feasibility which included the ability to recruit participants, deliver the intervention, retain patients in the study and collect meaningful data.

Adequate recruitment of participants is key to the success of any trial and is determined by factors such the suitability of inclusion criteria for the population to be screened, willingness of patients (or their next of kin) to enrol, the intervention (including an understanding of its potential benefits and harms) and the method and duration of data collection / sample collection. Recruitment to this trial was considerably slower than was predicted, which led to the study being stopped before reaching the target number of participants. The original plan was to recruit 60 patients at two centres in 15 months; this equates to 4 patients per month. A total of 34 patients were recruited to the study at a mean rate of 1.7 per month. Recruitment rate was reviewed regularly during the study, both at Trial Management Group (TMG) and Trial Steering Committee (TSC) meetings. The factors highlighted to have contributed to the low recruitment rate would need to be fully addressed to improve recruitment in a future trial:

1. **Method of consenting participants**. The process of agreement to enter this trial was to seek approval from a patient's next of kin, referred to as a personal consultee. The reason for this is that most patients fulfilling the inclusion criteria for the trial lacked capacity due to their severity of illness and / or level of sedation. Discussing research with a patient's relatives soon after the patient has been admitted to an ICU with a life-threatening condition can be extremely distressing for some families. Many are unable to take on board complex information whilst under such considerable stress. For this reason, many families decline or ask for additional time to consider the enrolment process, which would place the patient outside of the time-frame of recruitment for the study. Many trials of emergency therapy, especially in ICU, now use a model of deferred consent in which the patient is recruited into the trial as soon as inclusion criteria are met and their family are informed at a later point in time. This approach was successful for a trial of conservative oxygenation in critically ill children in the UK[12] and in the recent ICU-ROX trial conducted in New Zealand and Australia.[7]

2. **Control (comparator) group parameters**. Whilst precisely defining an intervention is crucial, many trials fail to deliver a meaningful message because the comparator group did not represent usual or common practice. The efficacy of an intervention can be both under and over exaggerated by creating an unrealistic comparator. When this trial was conceived in 2015, it was common for oxygen to be titrated to achieve normal or supranormal levels of arterial oxygenation in mechanically ventilated patients.[4, 13] During the course of the trial, increasing awareness of the potential harm that may be caused by hyperoxaemia in critically ill patients[14] led some clinicians at the two recruitment centres to feel uneasy enrolling patients into a trial in which the control group must have an SpO_2 of ≥ 96%. This was felt to have a detriment impact on patient enrolment. On advice from the TSC we therefore removed the SpO_2 ≥ 96% criteria from the control group of the study, allowing clinicians to select whatever oxygenation target they thought appropriate. Of note, a recent analysis of 29,657 index ICU patient episodes conducted from 2014-19 in England demonstrated an overall average SpO_2 of 96.2%[15] which was similar to the average SpO_2 of 97% in the control group in the present study.

3. **Low number of recruitment sites**. Due to constrains of funding we were only able to register two recruitment sites for this feasibility study. One of the sites encountered logistical issues during the recruitment period resulting in effectively only one site being able to actively recruit for a number of months. With hindsight, this feasibility study should have been designed with more recruitment centres. Whilst two additional recruitment sites were identified during the study, the process of adding these sites to the study was excessively lengthy and eventually both sites took the decision not to join the study.

4. **Inclusion and exclusion criteria**. As a feasibility trial, and the first time that conservative oxygenation had been used as an intervention in mechanically ventilated

patients in the NHS, this was a cautious and restrictive study design. We sought only to recruit patients with a primary diagnosis of acute respiratory failure and opted for a long list of exclusion criteria. The reasons for this were to limit the trial to those in whom hypoxaemia was likely to be a part of their presenting complaint (respiratory failure) and to avoid any unnecessary exposure to potential harm in groups of patients that may be susceptible to moderate hypoxaemia (e.g. haemorrhage or anaemia). One of the excluded cohorts was patients who had been admitted to ICU following a cardiac arrest. The reason for this was that it was hypothesised that hypoxaemia may reduce cerebral oxygenation and lead to harm. However, sub-group analysis of data from the ICU-ROX trial and a subsequent meta-analysis show that this hypothesis may have been incorrect.[7, 16]

In summary, a future trial of conservative oxygenation in an NHS setting should consider broad inclusion and minimal exclusion criteria, an unrestricted usual care comparator group, a deferred consent model for enrolment and a large number of simultaneously recruiting sites.

The intervention was halted prematurely (outside of a protocolised reason to end the intervention period) in a total of 10 (29.4%) patients. The commonest reason (40%) was a clinician withdrawing the patient from the study. In these cases, clinicians expressed concerns regarding oxygenation in both the conservative oxygenation (20% of clinician withdrawals) and control (20%) groups. This was an unexpected finding and efforts to rectify concerns in the control arm of the study led to the protocol change outlined above. Adherence to the designated SpO_2 targets was comparable between the two groups (Figure e2) and achieved for the majority of the time. Separation of oxygenation measures between the randomisation groups was good, as highlighted in Table 5 and Figures e1-4. There was a difference of 3.2 kPa between median PaO_2 values in the conservative and usual practice

groups (Table 7), which compares to 1.6 kPa in the recently published ICU-ROX trial.[7] Of note, this was achieved despite only a small difference between median FIO_2 in the two groups of our study (0.35 versus 0.37 in conservative and usual care groups respectively) (Table 5).

This study was not powered to formally assess the safety and efficacy of the intervention as compared to practice in the control group. The values in Table 6 show a trend toward better survival in the control group, accompanied by a shorter ICU length of stay; along with a similar pattern for hospital survival and length of stay. Whilst it is impossible to place any meaning to these findings due to the design of this study, it is noteworthy that a recent trial of conservative oxygen therapy (target SpO_2 88-92% in patients with ARDS reported a 28 day mortality of 34.3% in the conservative oxygen group and 26.5% in the 'liberal' oxygen group (SpO_2 ≥96%), a difference of 7.8 % (95% confidence interval -4.8 to 20.6).[8] The trial was stopped early by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups for the primary outcome.

Many of the limitations of this study design have been outlined above. The purpose of the study was to determine whether patients could be enrolled into a trial that delivered an intervention to generate separation in terms of delivered oxygen concentration and arterial oxygenation. An additional limitation was what appeared to be a high degree of missing data in this study (Table e1 in the online supplementary information). Many of the missing figures were due to these data not being part of routine ICU data capture at the frequency stated in the CRF. For example, the high degree of missing values for arterial blood gases is because they are not routinely taken hourly; they tend to be taken 4-6 hourly, at the discretion of the clinical team. Finally, the administration of oxygen therapy cannot be delivered in a blinded manner, therefore it is possible that knowledge of group allocation could have led to bias in the study results.

CONCLUSION

Whilst this trial was feasible in an NHS setting, it would require a number of fundamental alterations to the design of the study in order for it to be successful on a larger scale. There remains no answer to the question of whether a conservative oxygen intervention is beneficial to mechanically ventilated ICU patients, nor the precise SpO_2 target for the intervention. The methodology of this feasibility study delivered a clear separation of SpO_2 and PaO_2 between the intervention group and the control groups.

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DISCLAIMER

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TABLES

Table 1. Primary respiratory diagnosis of study participants at enrolment

Pneumonia	27 (79.4%)
Pulmonary oedema	3 (8.8%)
Pleural effusion	3 (8.8%)
Pneumonitis	1 (2.9%)

Table 2. Underling comorbidities of participants at enrolment

Cardiovascular disease	19 (55.9%)
Chronic lung disease	4 (11.8%)
Cancer	4 (11.8%)
Chronic kidney disease	3 (8.8%)
Chronic liver disease	7 (20.6%)
Immunosuppressed	5 (14.7%)

Table 3. Baseline respiratory characteristics of all participants

	median (IQR)
PaO_2 (kPa)	11.4 (10.0-13.1)
$PaCO_2$ (kPa)	5.3 (5.0-6.2)
SpO_2 (%)	95 (93-97)
F_IO_2	0.43 (0.35-0.50)
Tidal volume (ml)	522 (455-620)
Mean inspiratory pressure (cmH_20)	11 (10-13)
Peak inspiratory pressure (cmH_20)	25 (20-29)
Positive end expiratory pressure (PEEP) (cmH_2O)	10 (8-12)
Total SOFA Score	11 (9-13)
Total APACHE II Score	23 (17-29)

Table 4. Reasons for terminating the intervention

Reason for stopping intervention	**n**
Extubation*	17
Tracheostomy*	4
Death*	3
Relatives withdrew patient from the study	2
Clinicians withdrew patient from study	4
Withdrawal of treatment in ICU initiated	3
Transfer of patient to another hospital**	1

* predetermined stop points for the intervention.

** specified in the protocol as no ethics permission in receiving hospital.

Table 5. Treatment time-weighted averages [median (IQR)]

Randomised treatment	**F_IO_2**	**SpO_2 (%)**	**PaO_2 (kPa)**	**$PaCO_2$ (kPa)**
Conservative oxygen therapy	0.35 (0.25-0.48)	91 (90-92)	8.6 (8.0-9.4)	5.6 (5.1-6.2)
Control group	0.37 (0.30-0.52)	97 (96-97)	11.8 (10.3-14.0)	5.4 (4.9-6.1)

Table 6. A summary of key clinical outcomes by randomisation group

Clinical outcome	Randomised allocation	
	Conservative oxygenation group (n=17)	Control group (n=17)
Final ICU outcome [Alive] (%)	11 (64.7)	12 (70.6)
ICU length of stay (hours) [median (IQR)]	362 (244-787)	303 (194-601)
Final hospital outcome [Alive] (%)	10 (58.8)	12 (70.6)
Hospital length of stay (days) [median (IQR)]	43 (21-66)	25 (18-39)
Survival at 30 days [Alive] (%)*	11 (68.8)	12 (70.6)
Survival at 90 days [Alive] (%)**	9 (56.2)	11 (68.8)

* Information is missing from one participant in the conservative group
** Information is missing from one participant in the conservative group and one in the control group.

Table 7. Separation of intervention groups in terms of arterial partial pressure of oxygen for recent trials of conservative oxygen therapy

TRIAL	Intervention group	Target SpO_2	Median PaO_2 (kPa)	Group PaO_2 separation (kPa)
This study (Martin et al.)	Conservative O_2	88-92%	8.6	3.2
	Control	Usual care	11.8	
Girardis et al.[6]	Conservative O_2	94-98%	11.6	2.0
	Control	Usual care	13.6	
Mackle et al.[7]	Conservative O_2	91-96%	10.9*	1.6
	Control	≥91%	12.5*	
Barrot et al.[8]	Conservative O_2	88-92%	9.3*	4.6
	Control	≥96%	13.9*	

* converted to kPa if expressed as mmHg

Median PaO_2 and group separation in controlled trials of conservative oxygen therapy in Critical Care settings. The values for means for Mackle et al and Barrot et al's studies were estimated from graphs in supplemental appendices provided with the manuscripts.

ONLINE SUPPLEMENTARY INFORMATION

Table e1. Summary of missing data by randomised treatment

CRF	Conservative oxygenation	Usual care
01.0 Registration	0	0
02.0 Diagnosis	0	0
03.0 Medical History	0	0
04.1 Eligibility & Randomisation (Sealed Envelope) SE	0	0
04.2 Randomisation	0	0
05.1 & 05.2 APACHE II Score components	1	0
06.1 & 06.2 SOFA	0	0
07.1 & 07.2 & 07.3 Clinical Data I (Pre–Intervention)		
PaO2 (kPa)	0	2
PaCO2 (kPa)	0	2
Mean inspiratory pressure (cmH_20)	13	15
Peak inspiratory pressure (cmH_20)	0	1
Positive End Expiratory Pressure (PEEP) (cmH_2O)	0	1
Mean airway pressure (cmH_2O)	1	5
Richmond Agitation Sedation Scale (RASS) Score	1	0
Alanine transaminase (ALT) (IU/L)	0	1
Aspartate transaminase (AST) (IU/L)	7	7
Prothrombin time (PT) (sec)	7	7
Activated Partial Thromboplastin Time (APTT) (sec)	7	7
08.1 & 08.2 Clinical data II (Oxygen Measurements)		
F_IO_2 (%)	32	33
SpO_2 (%)	38	27
PaO_2 (kPa)	420	524
$PaCO_2$ (kPa)	424	524
Number of hours 100% Oxygen boluses per day	2	1
09.1 to 09.4 Clinical Data III (Bloods & Clinical Assessment)	2	3
Haemoglobin concentration (g/L)	2	3
Creatinine (µmol/L)	3	3

Platelet count (x10 /L)	2	3
Total Bilirubin (µmol/L)	3	3
Lactate (mmol/L)	2	3
pH	2	10
Alanine aminotransferase (ALT) (IU/L)	44	54
Aminotransferase (AST) (IU/L)	43	51
Prothrombin time (PT) (sec)	44	50
Activated Partial Thromboplastin Time (APTT) (sec)	2	3
Mean arterial pressure (MAP) (mmHg)	2	3
Heart rate (beats per minute)	2	3
Number of packed red cells in the last 24 hours	2	3
Mode of mechanical ventilation	2	3
Total respiratory rate (breaths per minute)	3	3
Tidal volume (ml)	92	113
Mean inspiratory pressure (cmH_20)	3	4
Peak inspiratory pressure (cmH_20)	3	5
Positive End Expiratory Pressure (PEEP) (cmH_2O)	22	22
Mean airway pressure (cmH_2O)	3	4
Richmond Agitation Sedation Scale (RASS) Score	3	4
Glasgow Coma Scale (Score)	117	122
Fluid balance (ml)		
10.0 Blood sampling (Oxidative Stress) Day 2, 3, 5, 10		
Blood sample NOT taken	10	14
11.0 End of intervention & Participant consent	0	0
12.0 Survival Outcome		
Participants with NO data (TOX018032)	1	0
13.0 Adverse Events (AE)		
Participants with NO reported adverse events	5	5
14.0 Principal Investigator eSignoff		
Participants with no eSignoff	5	5

Table e2. Summary of adverse event data by randomised treatment

Adverse event data 24 participants had at least one AE	**Conservative oxygenaion** n=37	**Usual care** n=38
Organ system		
Respiratory	11	9
Cardiovascular	12	9
Haematological	2	2
Renal	4	3
Gastrointestinal	2	5
Neurological	4	6
Other	2	4
Event description		
Reintubation	1	2
Arterial desaturation	6	3
Arrhythmia	6	5
Requirement for inotropic support	0	1
Anaemia	1	0
Low platelet count	0	1
High white blood cell count	1	1
Acute kidney injury	2	1
Requirement for renal support	1	2
Diarrhoea	0	1
Failure to absorb enteral feed	0	1
Delirium	1	2
Other	18	18
Serious event?		
No	27	25
Yes	10	13
Event severity		
Mild	14	14
Moderate	15	16
Severe	8	8
Causality		
Not related	10	15
Unlikely	23	21
Possibly	3	1

Probably	1	0
Unknown	0	1
Expectedness		
Unexpected	21	23
Expected	15	12
Unknown	1	3
Outcome		
Resolved	14	18
Resolved with sequelae	3	4
Ongoing	15	12
Death	5	4

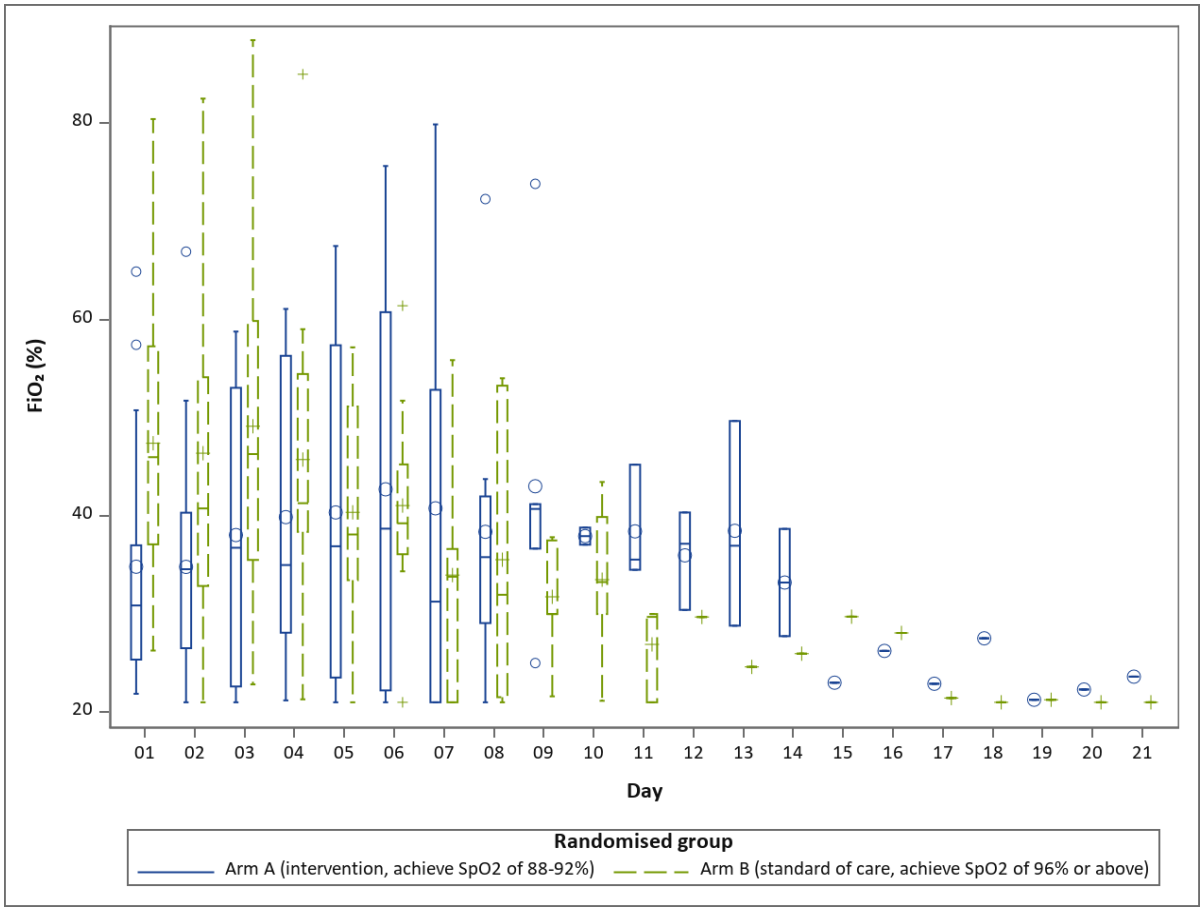
Table e3. Summary of protocol deviations

There were 22 protocol deviations in 15 participants:

- 19 procedure /assessment not done
- 1 procedure / assessment done, but out of window
- 2 others:
    - “Atrial fibrillation episode at 03:30 am, decision made to increase F_IO_2 to 40% by clinical team. Saturations were at 92%, PaO_2 at 9.1 kPa. Research team not informed. Saturations subsequently increased above target range. This was not followed for 3.5 hours. ICU research team discovered event at 07:00. DM (PI) present and informed of the situation, he discussed with the night team. Protocol recommenced.”
    - “Bloods taken at 11:11 am on 14/05/18 - in the study Day 2 window. Due to confusion over study days, the processed bloods were stored in aliquots labelled for Day 3 samples.”

Figure e1

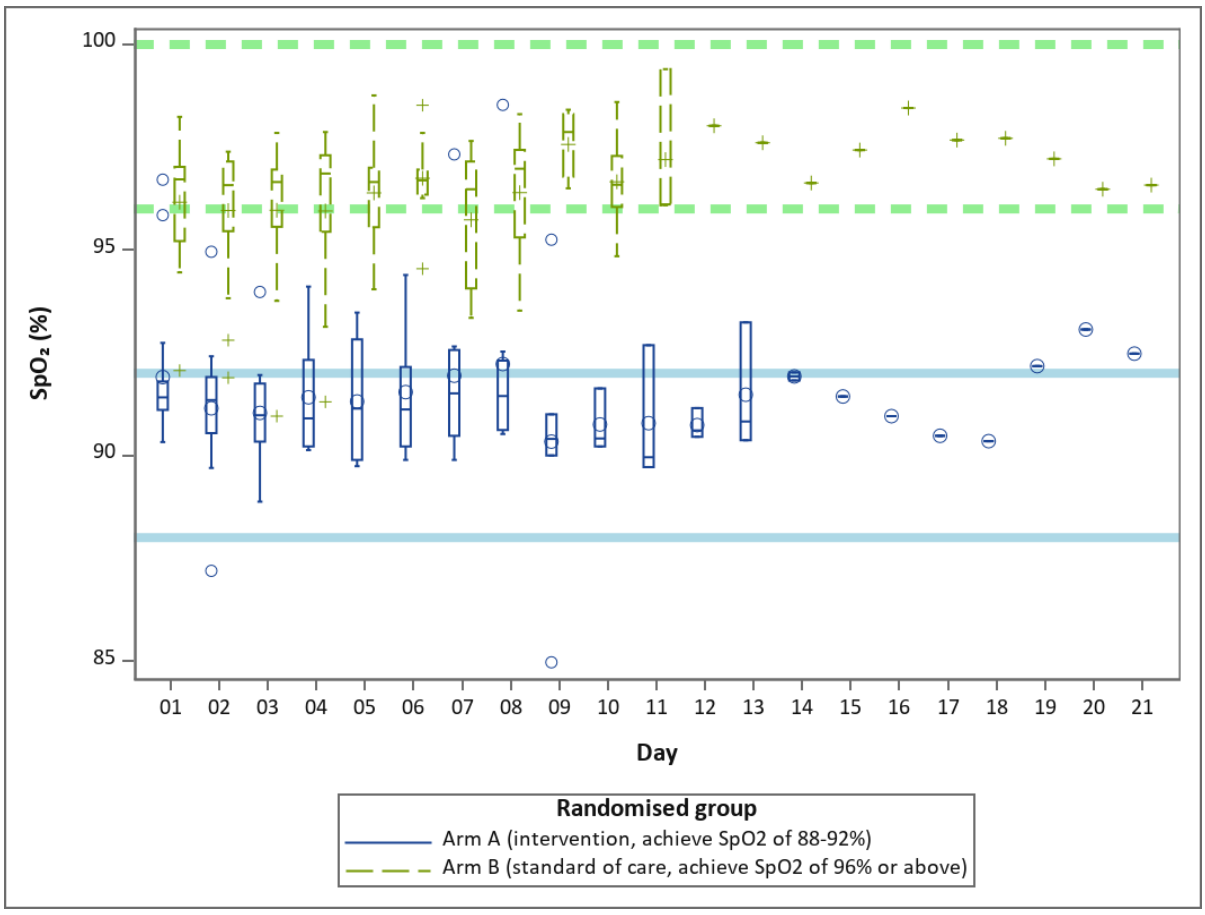
Daily time-weighted mean values for fractional inspired oxygen concentration in the conservative oxygen therapy and control groups



The bottom and top edges of the box indicate the intra-quartile range (IQR). The line inside the box indicates the median value. The marker inside the box indicates the mean value. The whiskers that extend from each box indicate the range of values that are outside of the intra-quartile range. However, they are close enough not to be considered outliers (a distance less than or equal to 1.5*IQR). Outliers are observations that are more extreme than the upper and lower whiskers (plus minus 1.5 IQR)

Figure e2

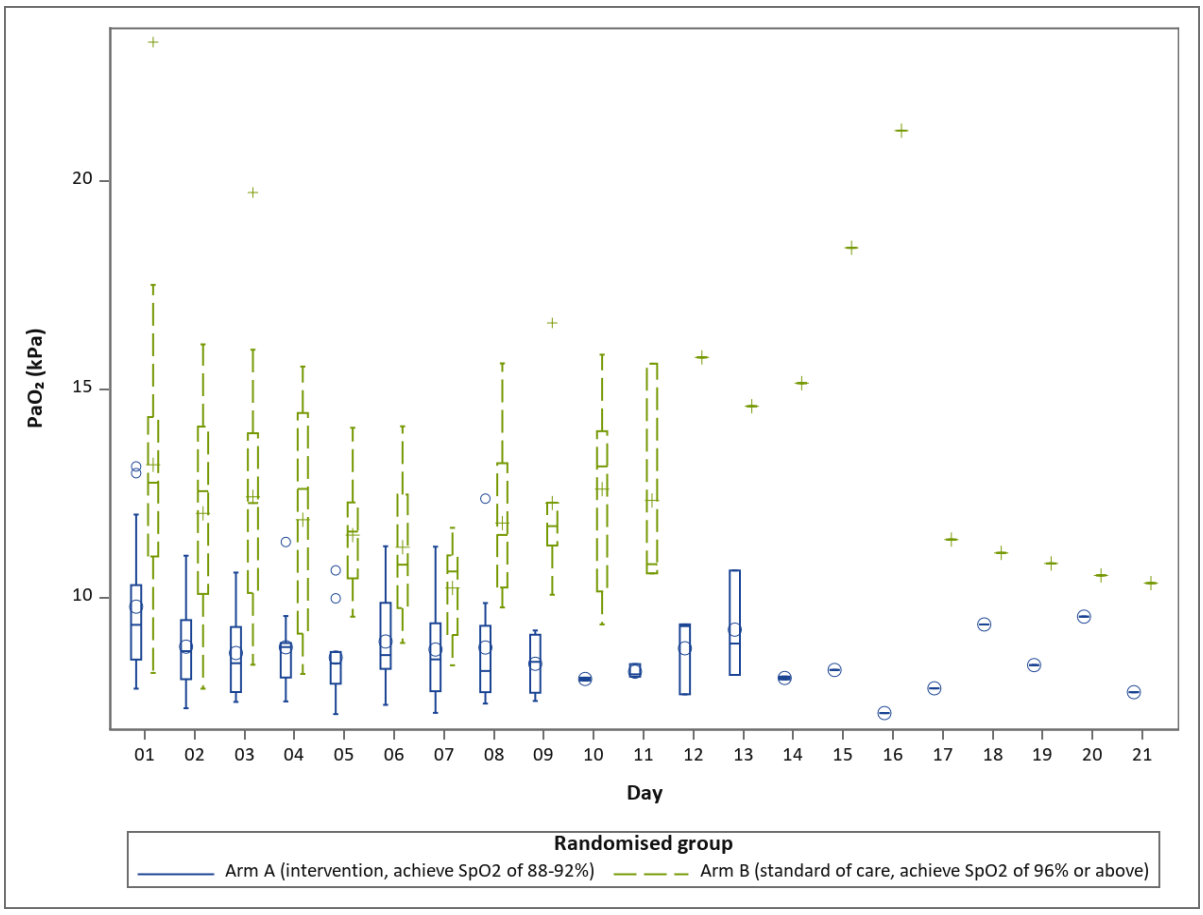
Daily time-weighted mean values for oxygen saturation in the conservative oxygen therapy and control groups.



The bottom and top edges of the box indicate the intra-quartile range (IQR). The line inside the box indicates the median value. The marker inside the box indicates the mean value. The whiskers that extend from each box indicate the range of values that are outside of the intra-quartile range. However, they are close enough not to be considered outliers (a distance less than or equal to 1.5*IQR). Outliers are observations that are more extreme than the upper and lower whiskers (plus minus 1.5 IQR). Horizontal lines show the protocol-specified minimum and maximum SpO_2 for each randomised arm (blue is intervention and green is control).

Figure e3

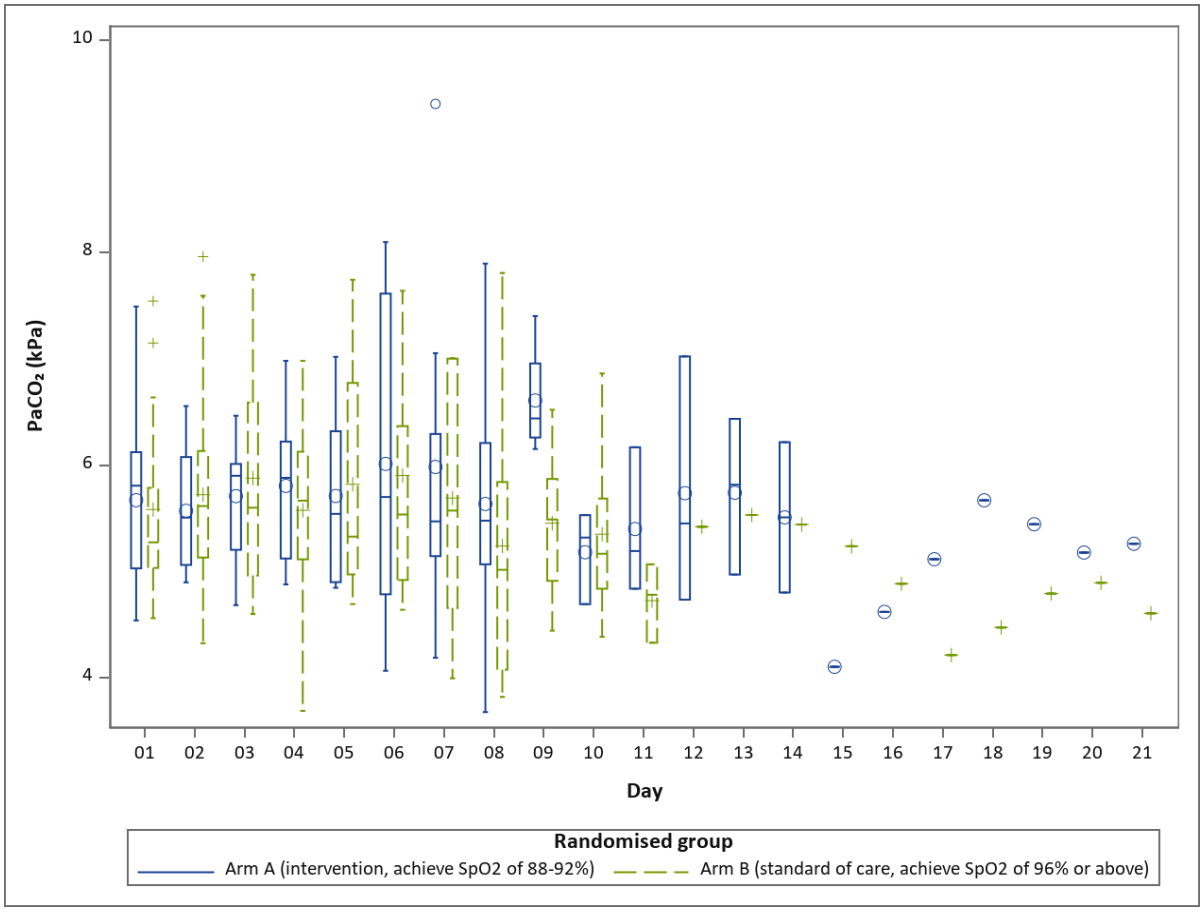
Daily time-weighted mean values for arterial partial pressure of oxygen in the conservative oxygen therapy and control groups



The bottom and top edges of the box indicate the intra-quartile range (IQR). The line inside the box indicates the median value. The marker inside the box indicates the mean value. The whiskers that extend from each box indicate the range of values that are outside of the intra-quartile range. However, they are close enough not to be considered outliers (a distance less than or equal to 1.5*IQR). Outliers are observations that are more extreme than the upper and lower whiskers (plus minus 1.5 IQR)

Figure e4.

Daily time-weighted mean values for arterial partial pressure of carbon dioxide in the conservative oxygen therapy and control groups



The bottom and top edges of the box indicate the intra-quartile range (IQR). The line inside the box indicates the median value. The marker inside the box indicates the mean value. The whiskers that extend from each box indicate the range of values that are outside of the intra-quartile range. However, they are close enough not to be considered outliers (a distance less than or equal to 1.5*IQR). Outliers are observations that are more extreme than the upper and lower whiskers (plus minus 1.5 IQR)

REFERENCES

1. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med. 2013;41:423-432.
2. de Jonge E, Peelen L, Keijzers PJ et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12(6):R156.
3. Schjørring OL, Jensen AKG, Nielsen CG et al. Arterial oxygen tensions in mechanically ventilated ICU patients and mortality: a retrospective, multicentre, observational cohort study. Br J Anaesth. 2020;124:420-429.
4. Eastwood G, Bellomo R, Bailey M et al. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med. 2012;38:91-98.
5. Palmer E, Post B, Klapaukh R et al. The Association between Supraphysiologic Arterial Oxygen Levels and Mortality in Critically Ill Patients. A Multicenter Observational Cohort Study. Am J Respir Crit Care Med. 2019;200:1373-1380.
6. Girardis M, Busani S, Damiani E et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA. 2016;316:1583-1589.
7. Mackle D, Bellomo R, Bailey M et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020;382:989-998.
8. Barrot L, Asfar P, Mauny F et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. New England Journal of Medicine. 2020;382:999-1008.
9. Chan AW, Tetzlaff JM, Altman DG et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:200-207.
10. Martin DS, Brew-Graves C, McCartan N et al. Protocol for a feasibility randomised controlled trial of targeted oxygen therapy in mechanically ventilated critically ill patients. BMJ Open. 2019;9:e021674.

11. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol. 2010;10:67.
12. Peters MJ, Jones GAL, Wiley D et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. Intensive Care Med. 2018;44:1240-1248.
13. Helmerhorst HJ, Schultz MJ, van der Voort PH et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. Ann Intensive Care. 2014;4:23.
14. Martin D, Grocott M. Oxygen therapy and the Goldilocks principle. J Intensive Care Soc. 2017;18:279-281.
15. Post B, Palmer E, Harris S et al. Oxygenation of the critically ill in selected intensive care units in the UK: are we usual. Br J Anaesth 2020;125(3):E277-279.
16. Young PJ, Bailey M, Bellomo R et al. Conservative or liberal oxygen therapy in adults after cardiac arrest: An individual-level patient data meta-analysis of randomised controlled trials. Resuscitation. 2020;157:15-22