

Conservative Oxygen Therapy in Mechanically Ventilated Critically

III Adult Patients: The UK-ROX Randomized Clinical Trial

Authors: Daniel S. Martin, PhD^{1,2}; Doug W. Gould, PhD³; Tasnin Shahid, BSc³; James C. Doidge, PhD³; Alex Cowden, MSc³; Zia Sadique, PhD⁴; Julie Camsooksai, BSc³; Walton N. Charles, MSc³; Miriam Davey, PGDip⁵; Amelia Francis Johnson, MSc³; Roger M. Garrett, PhD⁶; Michael P. W. Grocott, MD⁷; Joanne Jones, RN⁵; Lamprini Lampro, MSc³; Diane M. Mackle, PhD⁸; B. Ronan O'Driscoll, MD⁹; Alvin Richards-Belle, BSc³; Anthony J. Rostron, PhD¹⁰; Tamas Szakmany, PhD¹¹; Alex Warren, MBBS^{3,12,13}; Paul J. Young, MD, PhD^{14,15,16}; Kathryn M. Rowan, PhD³; David A. Harrison, PhD³; Paul R. Mouncey, MSc³ on behalf of the UK-ROX Investigators

Authors' affiliations are listed at the end of the manuscript

Corresponding author:

Daniel S. Martin

Peninsula Medical School, University of Plymouth

John Bull Building, 16 Research Way

Plymouth, PL6 8BU

United Kingdom

Email: daniel.martin@plymouth.ac.uk

Word count (abstract): 344

Word count (main manuscript): 3504

Date of revision: 20 May 2025

24 **KEY POINTS**

25 **Question**

26 Does reducing exposure to supplemental oxygen through a strategy of conservative oxygen
27 therapy by using a peripheral oxygen saturation (SpO₂) target of 90% (range 88-92%)
28 reduce 90-day all-cause mortality in mechanically ventilated adult patients receiving
29 supplemental oxygen in intensive care units?

30 **Findings**

31 In this randomized clinical trial of 16 500 participants, there was no statistically significant
32 difference between the groups with 35.4% of patients randomized to conservative oxygen
33 therapy having died by 90 days compared with 34.9% of patients receiving usual oxygen
34 therapy.

35 **Meaning**

36 The findings do not support an approach of reducing oxygen exposure by targeting an SpO₂
37 of 90% in mechanically ventilated adults receiving oxygen on an intensive care unit.

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ABSTRACT

Importance

Supplemental oxygen is frequently given to patients in intensive care units (ICUs); however, there is insufficient evidence to guide its therapeutic use and to minimize the potential harm caused by administering too little or too much.

Objective

To determine whether reducing exposure to supplemental oxygen through a strategy of conservative oxygen therapy by using a peripheral oxygen saturation (SpO₂) target of 90% (range 88-92%) reduces mortality at 90 days in mechanically ventilated adult patients receiving supplemental oxygen in the ICU.

Design, Setting and Participants

Multi-center, pragmatic, randomized clinical trial conducted in 97 ICUs in the United Kingdom including 16 500 mechanically ventilated patients receiving supplemental oxygen. Participants were enrolled between May 2021 and November 2024. Follow-up was completed in February 2025.

Interventions

Participants randomized to conservative oxygen therapy (n=8258) received the lowest fraction of inspired oxygen possible to maintain their SpO₂ at 90%. Participants randomized to usual oxygen therapy (n=8242) received oxygen therapy at the discretion of the treating clinician.

Main Outcomes and Measures

The primary outcome was all-cause mortality at 90 days. Secondary outcomes included duration of ICU and acute hospital stay among survivors, days alive and free from organ support at 30 days, and mortality at other timepoints.

Results

Of 16 500 randomized patients, primary outcome data were available for 16 394 (8211 in the conservative and 8183 in the usual oxygen therapy group). Randomized groups were similar, with a median (IQR) age of 60 (48-71) and 38.2% females in both groups. Exposure to supplemental oxygen was 29% lower for participants in the conservative oxygen therapy group compared with the usual oxygen therapy group. By 90 days, 2908 (35.4%) participants in the conservative oxygen therapy group had died compared with 2858 (34.9%) in the usual oxygen therapy group. After adjustment for pre-specified baseline variables, this gave a risk difference of 0.7 percentage points (95% CI -0.7 to 2.0; $P=.28$).

Conclusions and Relevance

In adult ICU patients receiving mechanical ventilation and supplemental oxygen, minimizing oxygen exposure through conservative oxygen therapy did not significantly reduce all-cause mortality at 90 days.

Trial Registration: [ISRCTN13384956](https://www.clinicaltrials.gov/ct2/show/study?term=SRCTN13384956&rank=1)

INTRODUCTION

Oxygen is one of the most commonly administered drugs to patients in intensive care units (ICUs).¹ Traditionally, hypoxemia was avoided to minimize the risk of causing cellular hypoxia and organ dysfunction. In response to this, a liberal approach to oxygen therapy was commonplace for critically ill patients,² however, excessive administration of supplemental oxygen may also lead to harm.³ Achieving a balance between too little and too much oxygen could therefore be essential to optimize clinical outcomes for patients.

Clinical trials to date have been unable to determine whether administering less, rather than more, oxygen to patients is beneficial. Several clinical trials have shown no difference in outcome between a conservative compared with a more liberal approach to oxygen therapy in critically ill patients.⁴⁻⁸ However, in patients admitted to ICU with COVID-19 and severe hypoxemia, conservative oxygen therapy resulted in more days alive without life support in ICU.⁹ Moreover, in mechanically ventilated children receiving supplemental oxygen in a pediatric ICU, conservative oxygen therapy resulted in a reduction in a composite of organ support at 30 days or death.¹⁰ A recent systematic review and meta-analyses of 13 clinical trials including 10 632 adult patients reported no significant mortality difference between conservative and liberal oxygen therapy.¹¹ For such a widely used intervention, even a small survival benefit could translate into large numbers of lives saved. Therefore, further evidence from large-scale trials is required to determine whether conservative oxygen therapy is beneficial to patients receiving mechanical ventilation.

The UK-ROX randomized clinical trial assessed whether reducing exposure to supplemental oxygen through a strategy of conservative oxygen therapy by targeting a peripheral oxygen saturation (SpO₂) of 90% (range 88-92%) reduced mortality at 90 days, when compared with usual oxygen therapy, in mechanically ventilated adults receiving supplemental oxygen in the ICU.

106 **METHODS**

107 Trial Design and Oversight

108 UK-ROX was a multi-center, pragmatic, registry-embedded, randomized clinical trial (RCT).
109 The protocol was approved by the South Central – Oxford C Research Ethics Committee
110 (Reference: 20/SC/0423) and the UK Health Research Authority and has been published
111 previously.¹² The UK National Institute for Health and Care Research (NIHR) funded the trial.
112 The Intensive Care National Audit & Research Centre (ICNARC) Clinical Trials Unit
113 managed the trial, with independent oversight by a trial steering committee and a data
114 monitoring and ethics committee. The trial is reported in accordance with the CONSORT
115 2010 statement on reporting guidelines for parallel-group randomized trials.¹³

116 Trial Sites and Study Population

117 The trial was conducted in 97 National Health Service (NHS) adult, general ICUs that
118 participate in the Case Mix Programme (CMP) national clinical audit for adult ICUs in
119 England, Wales and Northern Ireland. The study population comprised critically ill adults
120 aged ≥ 18 years, enrolled within 12 hours of meeting the following criteria: receiving invasive
121 mechanical ventilation following an unplanned admission to ICU or where invasive
122 mechanical ventilation was started in the ICU; and receiving supplemental oxygen. Patients
123 were excluded if randomized to UK-ROX in the previous 90 days, if in receipt of
124 extracorporeal membrane oxygenation, or if the treating clinician considered that the
125 intervention was either clinically indicated or contraindicated.

126 Randomization and blinding

127 Randomization occurred as soon as possible after confirmation of eligibility. Participants
128 were allocated 1:1, via a concealed central 24-hour telephone/web randomization system, to
129 conservative oxygen therapy or usual oxygen therapy. Randomization used permuted blocks
130 with variable block sizes, stratified by site and the following (hierarchical) diagnostic

subgroups: hypoxic-ischemic encephalopathy (HIE); sepsis; acute brain injury (except HIE); or none of the pre-specified subgroups, as defined by the treating clinician. Treatment allocation was not blinded.

Interventions

Aiming to minimize exposure to supplemental oxygen, participants in the conservative oxygen therapy group received the lowest fraction of inspired oxygen (FiO_2) of oxygen possible to maintain their pulse oximeter derived SpO_2 at 90%. Sites were instructed to set monitor alarms to sound below 88% and above 92%, once the patient was within range. The upper limit alarm could be deactivated once the patient was receiving an FiO_2 of 0.21. Deviations were allowed if: there were major discrepancies with the arterial blood gas derived oxygen saturation (SaO_2) and the SpO_2 ; a high FiO_2 was needed to prevent an acute life-threatening illness; or a change in clinical circumstances occurred that would have precluded eligibility to the trial. Adherence to the conservative oxygen therapy group was defined as a reduction in supplemental oxygen when the SpO_2 was above 92% or an increase in oxygen when below 88%. Clinicians were permitted to alter other therapies as required. Full descriptions of the assessment of treatment exposure and adherence are in Supplement 2 page 3.

In the usual oxygen therapy group, participants received supplemental oxygen at the discretion of the treating clinician. No minimum FiO_2 was mandated and no upper SpO_2 limit monitor alarm was set. Interventions were continued until 90 days post-randomization or discharge from ICU, whichever was sooner. If readmitted to the ICU during this time period, units were advised to recommence.

Consent procedures

In accordance with the approved emergency waiver of consent under the relevant Mental Capacity Acts in England and Wales and in Northern Ireland, a 'research without prior consent' approach was used, which allowed agreement to be obtained from a personal or

nominated consultee as soon as appropriate following randomization. If the patient regained mental capacity, informed consent was obtained. If the patient had capacity prior to randomization, verbal consent could be obtained. All data collected up to refusal or withdrawal of consent were retained. In addition, approvals were obtained to allow the primary outcome to be collected on all participants, other than those who requested that all data be removed. Secondary outcomes were available for those who provided consent to allow data linkage. All procedures are in Supplement 2 pages 4-6.

Outcome measures

The primary outcome was all-cause mortality at 90 days after randomization. Secondary outcomes were: duration of ICU and acute hospital stay (censored at 90 days); days alive and free from organ support (respiratory, cardiovascular or renal support) at 30 days; mortality at ICU and hospital discharge (censored at 90 days); and 60-day and one-year mortality. All definitions are in Supplement 2 pages 7-8. The integrated health-economic evaluation will be reported separately.

Sample size calculations

Based on CMP data (N=96 028, April 2017 to March 2019) and the Risk II study dataset (N=82 075, April 2014 to March 2016),¹⁴ 90-day all-cause mortality was anticipated to be 37% for usual oxygen therapy. Assuming 6% loss to follow-up, a sample size of 16 500 provided 90% power at $P<.05$ to detect an absolute risk reduction of 2.5 percentage points to 34.5% with conservative oxygen therapy. Two interim analyses were performed after 4500 and 10 000 participants using a Peto-Haybittle stopping rule ($P<.001$) for effectiveness or harm.

Data collection

For efficiency of trial delivery, the majority of data were obtained from linked, routine data sources: the CMP (for baseline data, ICU and hospital outcomes) and Civil Registrations of

Death (for mortality post-hospital discharge).¹⁵ To understand oxygen administration and adherence to the intervention, SpO₂ and FiO₂ were collected hourly on a sample of enhanced data collection participants for ten days post-randomization. Total exposure to supplemental oxygen was calculated by the amount administered above room air (FiO₂ of 0.21). For example, one hour on FiO₂ = 1.0 or two hours on FiO₂ = 0.605 are calculated as one 100%-equivalent hour as both equate to an additional 79% of oxygen (the maximum for a single hour). Enhanced data were collected for approximately 15% of participants: the first ten participants at each site, to ensure the protocol was being adhered to, followed by a random sample of 10% of subsequent participants. If adherence was deemed unacceptable, enhanced data collection was extended.

Statistical Analysis

Participants were analyzed according to their randomized group, following a pre-specified statistical analysis plan (Supplement 1). All statistical tests were two-sided with significance set at $P < .05$ unless otherwise specified. Effect estimates are reported with 95% confidence intervals (CI). There was no adjustment for multiple testing.

The primary analyses were adjusted for the stratification variables (site; and diagnostic subgroup) and for additional pre-specified baseline covariates that were deemed strong predictors of outcome (age; SpO₂ at randomization; PaO₂/FiO₂ ratio at randomization; confirmed/highly suspected COVID-19; and date of randomization). Effects were estimated using logistic regression for binary outcomes, Fine-Gray subdistribution hazards regression for durations of ICU and hospital stay among survivors (with death as a competing risk), and ordered logistic regression for days alive and free of organ support. Time to death was analyzed using Cox proportional hazards regression with censoring at the earliest of withdrawal, 365 days or the end of trial. All models accounted for clustering by site, and were adjusted for diagnostic subgroup (stratification variable) and for the same pre-specified baseline predictors of outcome. Risk differences and relative risks were estimated using marginal standardization.¹⁶ Multivariate imputation by chained equations was used to

account for missing data, incorporating at least the primary outcome as an auxiliary variable to support imputation of secondary outcomes.

The primary outcome was also analyzed by pre-specified subgroups (diagnostic subgroup; confirmed/highly suspected COVID-19 versus not; and ethnic group). For each subgroup, the primary outcome analysis was repeated including an interaction between conservative oxygen therapy and the subgroup variable (for multinomial subgroup variables, one interaction term for each dummy variable). Subgroup effects were tested (jointly for any subgroup variables with more than two categories) on the odds ratio (OR) scale.

Additional post hoc analyses included subgroup analyses by severity of illness (tertile of predicted risk of death; tertile of Acute Physiology And Chronic Health Evaluation [APACHE] II score;¹⁷ and categories of PaO₂/FiO₂ ratio aligned with acute respiratory distress syndrome definitions)¹⁸ and by data collection subset (first ten patients and random enhanced data collection sample versus standard data collection).

All statistical analyses were conducted in Stata/MP version 18.0 (StataCorp).¹⁹

RESULTS

Sites and Participants

A total of 52 747 critically ill patients receiving invasive mechanical ventilation were screened at the 97 sites between 4 May 2021 and 27 November 2024, of whom 38 479 were potentially eligible and 16 500 were enrolled (Figure 1 and eFigure 1 and eTable 1 in Supplement 2). Sixty-six participants (0.4%) requested removal of all data and were excluded from the analysis. The primary outcome was unable to be determined for a further 40 participants (0.2%), as data could not be linked, who remained in the multiply imputed primary analysis of 16 434 participants (8230 conservative oxygen therapy, 8204 usual oxygen therapy; 8211 and 8183 with primary outcome recorded, respectively). Ninety-day

follow-up was completed in February 2025, with linkage to death registrations conducted in March 2025, at which time 13 052 participants had reached 12 months' follow-up.

The randomized groups were similar at baseline (Table 1 and eTable 2 in Supplement 2) and were representative of the wider ICU population on key demographic factors (eTable 3 in Supplement 2). In both groups, the median (IQR) age was 60 (48-71) years and 38.2% were female. Participants were randomized shortly after first receiving invasive mechanical ventilation in ICU, with a median (IQR) time to randomization of 5 (2-8) hours in both groups. Prior to randomization, median (IQR) SpO₂ was 97% (94-99%) in the conservative oxygen therapy group and 96% (94-99%) in the usual oxygen therapy group. A total of 1504 (9.2%) were admitted due to HIE, 5443 (33.1%) due to sepsis, and 363 (2.2%) due to acute brain injury, with the remaining 9124 (55.5%) not in any of the pre-specified subgroups of interest. Of all participants, 1099 (6.7%) had confirmed or highly suspected COVID-19 on enrolment. Of the 16 434 participants included in the primary analysis, 2489 (1252 conservative oxygen therapy, 1237 usual oxygen therapy) were selected for enhanced data collection. Due to the timing of the start of the trial, there was a higher proportion of patients who had confirmed or highly suspected COVID-19 in the non-random first ten enhanced data collection patients from each site (13.4%) compared with the subsequent randomly selected patients (5.3%) and the standard data collection patients (6.4%). Otherwise, these groups were similar (eTable 4 in Supplement 2)

Oxygen exposure

Exposure to supplemental oxygen was lower for participants in the conservative oxygen therapy group, with a mean (SD) of the median FiO₂ of 0.31 (0.14) compared with 0.35 (0.15) for those in the usual oxygen therapy group. Total exposure to supplemental oxygen was 29.3% lower in participants in the conservative oxygen therapy group compared with participants in the usual oxygen therapy (20.3 vs 28.7 100%-equivalent hours, respectively;

difference -8.4 hours, 95% CI -10.8 to -6.0) (Figure 2 and eFigures 2 and 3 and eTable 5 in Supplement 2).

Arterial oxygenation was lower in the conservative oxygen therapy group with a mean (SD) of the median SpO₂ of 93.3% (2.8%) and mean (SD) of the median PaO₂ of 71.5 (13.9) mmHg compared with 95.1% (2.4%) and 79.5 (17.9) mmHg, respectively, for the usual oxygen therapy group. Participants in the conservative oxygen therapy group spent a mean (SD) of 62.6 (62.3) hours within the SpO₂ target range (88 to 92%) compared with 27.2 (39.1) hours for the usual oxygen therapy group. Whilst above the target range, a mean (SD) 39.7 (55.1) hours was spent on room air in the conservative oxygen therapy group, compared with 26.1 (45.1) hours in the usual oxygen therapy group. Participants had an SpO₂ below 88% for a mean (SD) of 3.2 (6.5) hours in the conservative oxygen therapy group and 2.3 (7.3) hours in the usual oxygen therapy group (Figure 2 and eFigures 2 and 3 and eTable 5 in Supplement 2). Separation was maintained across all enhanced data collection patient groups (eTable 6 in Supplement 2) and when plotted across calendar time and patient sequence to understand any potential contamination into usual care (eFigure 4 in Supplement 2).

Adherence to the Protocol

Of participants allocated to conservative oxygen therapy and selected for enhanced data collection, 526 (42.1%) had one or more periods of non-adherence, representing 10.6% of their time in ICU. There were a total of 2271 periods of non-adherence ≥3 hours. The main reasons included: staffing issues and lack of awareness, n=857; other clinical priorities, n=413; responding to low PaO₂, n=127; clinical decision to suspend intervention (not supported by the protocol), n=265; and reason not documented, n=609.

Primary and Secondary Outcomes

In the conservative oxygen therapy group, 2908 (35.4%) participants died compared with 2858 (34.9%) in the usual oxygen therapy group. After adjustment for pre-specified baseline

variables, this gave a risk difference of 0.7 percentage points (95% CI -0.7 to 2.0; $P=.28$) compared with an unadjusted risk difference of 0.5 percentage points (95% CI -1.0 to 2.0). (Table 2). There were no missing data among the baseline variables used for adjustment, other than for $\text{PaO}_2/\text{FiO}_2$ ratio which was singly imputed from $\text{SpO}_2/\text{FiO}_2$ ratio (eTable 7 in Supplement 2).

Secondary mortality outcomes at ICU discharge, 60 days and one year were not significantly different by treatment group (Table 2). Time to death (adjusted hazard ratio 1.01, 95% CI 0.96 to 1.05; eFigure 4 in Supplement 2), and duration of ICU and acute hospital stay among survivors were not significantly different between the groups. Survivors in the conservative oxygen therapy group stayed a median (IQR) of 20 (11-40) days in acute hospital compared to 21 (10-42) days in the usual oxygen therapy group (hazard ratio 0.98; 95% CI 0.94 to 1.02). Days alive and free from organ support at 30 days were not significantly different in the conservative oxygen therapy group compared to the usual oxygen therapy group (proportional OR 1.01; 95% CI 0.96 to 1.07) (Table 2 and eFigure 6 and eTable 8 in Supplement 2). In the conservative oxygen therapy group, 58 (0.7%) participants had serious adverse events reported compared to 29 (0.4%) in the usual oxygen therapy group (eTable 9 in Supplement 2).

Tests for interaction were not statistically significant for diagnostic subgroup, confirmed/highly suspected COVID-19 or ethnic group (Figure 3), or for post-hoc subgroups by severity of illness (eFigure 7 in Supplement 2). In the post-hoc analysis by data collection subgroup, there was weak evidence of increased harm from conservative oxygen therapy among the first ten patients in each site but no difference for the random enhanced data collection sample compared with standard data collection (eFigure 7 in Supplement 2).

DISCUSSION

In this RCT of mechanically ventilated critically ill adult patients receiving supplementary oxygen in UK ICUs, minimizing oxygen exposure through conservative oxygen therapy did

not reduce all-cause mortality at 90 days compared to usual oxygen therapy. The observed reduction in exposure to oxygen translated to a 0.7 percentage point adjusted absolute increase in mortality at 90 days with a 95% CI from a 0.7 percentage point reduction to a 2.0 percentage point increase. We found no significant differences in prespecified or exploratory subgroup analyses of the primary outcome or in any of the secondary outcomes.

The findings are consistent with other RCTs of conservative oxygen therapy reporting mortality⁴⁻⁸ and a recent systematic review and meta-analysis of trials.¹¹ The trial design differed from others by having a usual care comparator rather than protocolized liberal oxygen therapy. Prior data had shown that the average SpO₂ of adult ICU patients in the UK was approximately 96%²⁰ and the findings of our feasibility RCT indicated that clinicians would be unwilling to maintain a minimum FiO₂ in the comparator group.²¹ Arterial oxygenation data from the usual oxygen therapy group suggest a more conservative approach to oxygen administration than was observed in other countries in the last two decades.^{2,22} Our findings add to the understanding of oxygenation targets in critically ill patients by evaluating oxygen therapy in more participants than all prior trials combined. The results of an ongoing larger RCT comparing conservative oxygen therapy to protocolized liberal oxygen therapy (minimum acceptable FiO₂ of 0.3) are awaited.²³

The goal of conservative oxygen targets is to minimize exposure to oxygen, yet most trials haven't achieved their specified arterial oxygenation targets.²⁴ In part, this is because SpO₂ often exceeds the upper target limit, even when no additional oxygen is given. Separation was observed between groups in all oxygen metrics, however, it was smaller than reported in other similar trials (eTable 10 in Supplement 2). This was in part due to usual care being more conservative than liberal comparator groups in previous trials, potentially reflecting the more recent trend towards giving less oxygen in ICU.

It is plausible that oxygen therapy has a differing effect according to patients' characteristics.²⁵ Machine learning techniques have demonstrated that patients predicted to benefit from lower oxygenation targets had a higher prevalence of acute brain injury, whilst

patients predicted to benefit from higher targets had a higher prevalence of sepsis.²⁶ In a trial enrolling patients with COVID-19, a lower oxygenation target was beneficial.⁹ The direction of the signals detected in our COVID-19 and sepsis cohorts align with these. An analysis of heterogeneity of treatment effect in the UK-ROX trial using machine learning techniques was pre-specified in the statistical analysis plan and will be reported separately.

The trial has several strengths. The size of the trial ensured adequate power to detect the small absolute risk reduction hypothesized to be associated with conservative oxygen therapy. Additionally, the high precision of the results means that a clinically important reduction of mortality from conservative oxygen therapy is very unlikely. The trial benefited from an efficient design, using linkage to available registries to significantly reduce its cost, thereby supporting a large sample. This sample was highly representative of the whole potentially eligible UK ICU population enhancing generalizability. Patients were rapidly enrolled into the trial following eligibility, reducing the likelihood of inappropriate oxygen therapy on ICU prior to randomization.

Limitations

Like other trials of conservative oxygen therapy, clinicians and patients could not be blinded to treatment intervention, and other aspects of care were at the discretion of clinicians. However, the primary outcome of the trial is unlikely to be subjected to bias. Clinicians excluded a sizable proportion of potential participants due to the intervention being either indicated or contraindicated, which could have meant patients who may have benefited were not included. It also may reduce the generalizability of the findings. A proportionate approach to data collection was necessary to allow a trial of this size to be delivered; however, it means that oxygenation cannot be confirmed for all patients on the trial. The use of a usual care comparator, essential as clinicians were unwilling to give potentially unnecessary oxygen therapy, could increase the risk of contamination; however, we found no evidence of this as separation was sustained over the trial. Other than adjusting for baseline SpO₂ and

PaO₂/FiO₂ ratio, prior oxygen administration could not be accounted for and, for some patients, could have been significant. Regarding protocol adherence, among enhanced data patients, episodes of non-adherence occurred in 42.1%. However, these episodes accounted for a small proportion of ICU hours and overall separation on oxygen exposure between groups was substantial.

CONCLUSION

In mechanically ventilated adults admitted to an ICU, minimizing oxygen exposure by targeting an SpO₂ of 90% did not reduce all-cause mortality at 90 days compared to usual oxygen therapy.

Figure Legends/footnotes

Figure 1. Screening, randomization and follow-up

FiO₂, fraction of inspired oxygen

^a As assessed by the treating clinician

^b Commonly reported clinical decisions included: imminent extubation, imminent discharge/transfer, imminent death/treatment withdrawal

^c Approval to obtain anonymised primary outcome data without consent

^d 40 patients had data that was unable to be linked for the primary outcome (e.g. not an NHS patient)

^e 3382 patients had not reached 12 months

Figure 2. (A) Separation in fraction of inspired oxygen (FiO₂) and peripheral oxygen saturation (SpO₂) when receiving supplemental oxygen, (B) categorized SpO₂, and (C) cumulative exposure to supplemental oxygen over first 10 days after randomization.

d, days

Figure 3. Subgroup analyses of primary outcome

CI, confidence interval; HIE, hypoxic-ischemic encephalopathy.

^a Adjusted for site, diagnostic subgroup, age, SpO₂, PaO₂/FiO₂ ratio, confirmed/highly suspected COVID-19, and date of randomization

^b P value for test of interactions in the odds ratio in adjusted multilevel logistic regression model

399 **Tables**400 **Table 1.** Patient baseline characteristics by oxygen therapy group.

	Conservative oxygen therapy group (n = 8230)	Usual oxygen therapy group (n = 8204)
Age, median (IQR) [No.], y	60 (48-71) [8230]	60 (48-71) [8204]
Sex		
Female	2803/7340 (38.2)	2849/7465 (38.2)
Male	4537/7340 (61.8)	4616/7465 (61.8)
Ethnic group		
Asian	263/7340 (3.6)	243/7465 (3.3)
Black	138/7340 (1.9)	153/7465 (2.0)
Mixed	52/7340 (0.7)	60/7465 (0.8)
White	6072/7340 (82.7)	6207/7465 (83.1)
Other ^a or not stated	815/7340 (11.1)	802/7465 (10.7)
Body mass index, kg/m ²		
<18.5	264/7111 (3.7)	259/7225 (3.6)
18.5-<25	2291/7111 (32.2)	2299/7225 (31.8)
25-<30	2129/7111 (29.9)	2250/7225 (31.1)
30-<40	1918/7111 (27.0)	1881/7225 (26.0)
≥40	509/7111 (7.2)	536/7225 (7.4)
Pre-existing severe respiratory disease ^b	171/7310 (2.3)	172/7436 (2.3)
Prior length of hospital stay, median (IQR) [No.], d	1 (1-3) [7293]	1 (1-3) [7419]
Prior duration of invasive mechanical ventilation in ICU ^c , median (IQR) [No.], h	5 (2-8) [8230]	5 (2-8) [8204]
Current or suspected diagnosis ^d		
Sepsis	2738/8230 (33.3)	2705/8204 (33.0)
HIE	754/8230 (9.2)	750/8204 (9.1)
Acute brain injury (except HIE)	183/8230 (2.2)	180/8204 (2.2)
None of the pre-specified subgroups	4555/8230 (55.3)	4569/8204 (55.7)
Confirmed/highly suspected COVID-19	536/8230 (6.5)	563/8204 (6.9)
SpO ₂ , median (IQR) [No.], %	97 (94-99) [8230]	96 (94-99) [8204]
FiO ₂ , median (IQR) [No.]	0.45 (0.35-0.60) [8230]	0.45 (0.35-0.60) [8204]
PaO ₂ , median (IQR) [No.], mm Hg	90 (75-116) [7638]	89 (74-114) [7620]
PaO ₂ /FiO ₂ ratio, mm Hg		
≤100	933/7638 (12.2)	936/7620 (12.3)
>100-≤200	2635/7638 (34.5)	2664/7620 (35.0)
>200-≤300	1978/7638 (25.9)	1977/7620 (25.9)
>300	2092/7638 (27.4)	2043/7620 (26.8)
ICNARC _{H-2023} model predicted risk of death ^e , mean (SD) [No.]	0.35 (0.29) [6882]	0.34 (0.29) [7014]
APACHE II score ^f , median (IQR) [No.]	16 (12-21) [7317]	16 (12-21) [7437]

Values are No./Total no. (%) unless otherwise indicated.

APACHE II, Acute Physiology and Chronic Health Evaluation II; FiO₂, fraction of inspired oxygen; HIE, hypoxic-ischemic encephalopathy; ICNARC, Intensive Care National Audit & Research Centre; ICU, intensive care unit; IQR, interquartile range; PaO₂, partial pressure of oxygen in the arterial blood; SD, standard deviation; SpO₂, peripheral oxygen saturation.

SI conversion factors: To convert PaO₂ and PaO₂/FiO₂ ratio to kPa, multiply values by 0.133.

^a. Other includes those in the Chinese ethnic group, and those not in the groups otherwise listed, collected as per the National Health Service Data Dictionary definitions for 'Ethnic category'.

^b. Shortness of breath with light activity due to pulmonary disease and evident within the six months prior to admission.

^c. Calculated since admission to critical care.

^d. For stratified randomisation, hierarchical classification was used to select at most one subgroup for each patient (from highest to lowest priority: HIE, sepsis, acute brain injury except HIE).

415 e. $ICNARC_{H-2023}$ was calculated using physiological measures, age, past medical history,
416 dependency, cardiopulmonary resuscitation prior to admission, mechanical ventilation receipt,
417 source of and primary reason for admission. Other than PaO_2 and FIO_2 values (last prior to
418 randomisation), physiological measures reflect information from the first 24 hours in critical care.
419 f. APACHE II score (range, 0–71; higher scores indicate greater severity) was calculated using
420 physiological measures, age and previous health status. Other than PaO_2 and FIO_2 values (last
421 prior to randomization), physiological measures reflect information from the first 24 hours in
422 critical care.

423 **Table 2.** Primary and secondary clinical outcomes.

424

Outcome	Conservative oxygen therapy group	Usual oxygen therapy group	Adjusted effect estimate (available case) (95% CI) ^a	Adjusted effect estimate (multiply imputed) (95% CI) ^b	P value
Primary outcome					
90-d mortality, No./Total (%)	2908/8211 (35.4)	2858/8183 (34.9)	RD: +0.7 (−0.6 to +2.1)	RD: +0.7 (−0.7 to +2.0)	.28
			RR: 1.02 (0.98 to 1.06)	RR: 1.02 (0.98 to 1.06)	
			OR: 1.04 (0.97 to 1.11)	OR: 1.04 (0.97 to 1.11)	
Secondary outcomes					
Duration of ICU stay, d					
Overall, median (IQR) [No.]	6.6 (3.1 to 13.3) [7333]	6.8 (3.1 to 13.8) [7448]	--	--	
ICU survivors, median (IQR) [No.]	7.3 (3.6 to 14.9) [5211]	7.7 (3.8 to 15.3) [5290]	SHR: 1.00 (0.96 to 1.04)	sHR: 1.00 (0.96 to 1.04)	.97
ICU non-survivors, median (IQR) [No.]	4.9 (1.7 to 10.4) [2122]	4.6 (1.7 to 9.8) [2158]	--	--	
Duration of acute hospital stay, Median (IQR) [No.], d					
Overall, median (IQR) [No.]	14 (7 to 30) [7323]	14 (7 to 31) [7434]	--	--	
Hospital survivors, median (IQR) [No.]	20 (11 to 40) [4791]	21 (10 to 42) [4906]	sHR: 0.98 (0.94 to 1.02)	sHR: 0.98 (0.94 to 1.02)	.27
Hospital non-survivors, median (IQR) [No.]	7 (3 to 14) [2532]	7 (3 to 13) [2528]	--	--	
Days alive and free from organ support at 30 d, median (IQR) [No.], d ^c	16 (−1 to 25) [7327]	16 (−1 to 25) [7444]	POR: 1.00 (0.95 to 1.06)	POR: 1.01 (0.96 to 1.07)	.64
30-d mortality, No./Total (%)	2435/7449 (32.7)	2427/7573 (32.0)	--	--	
Days free from organ support at 30 d among survivors, median (IQR) [No.], d	23 (16 to 26) [4933]	23 (15 to 26) [5054]	--	--	
Mortality at ICU discharge, No./Total (%)	2122/7334 (28.9)	2161/7453 (29.0)	RD: +0.2 (−1.2 to +1.6)	RD: −0.1 (−1.3 to 1.1)	.94
Mortality at acute hospital discharge, No./Total (%)	2533/7335 (34.5)	2535/7458 (34.0)	RD: +0.9 (−0.6 to +2.3)	RD: +0.5 (−0.8 to +1.9)	.46
60-d mortality, No./Total (%)	2637/7449 (35.4)	2617/7573 (34.6)	RD: +1.1 (−0.2 to +2.5)	RD: +0.8 (−0.6 to 2.2)	.25
1-y mortality, No./Total (%)	2295/5636 (40.7)	2314/5755 (40.2)	RD: +1.0 (−0.7 to +2.6)	RD: +3.3 (−0.7 to 7.3)	.34

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426 CI, confidence interval; sHR: subdistribution hazard ratio calculated using the Fine and Gray method to account for competing risk of death; ICU, intensive
 427 care unit; IQR, interquartile range; OR: odds ratio; POR: proportional odds ratio; RD: risk difference; RR: risk ratio.
 428 ^{a.} Regression models adjusted for stratified randomization factors of ICU site and diagnostic stratum, plus confirmed/highly suspected COVID-19 and
 429 restricted cubic splines of age, SpO₂, PaO₂/FiO₂ ratio and date of randomization.
 430 ^{b.} Primary analysis: adjusted as above, with multiple imputation of missing data, except for duration of ICU and acute hospital stay, where patients with
 431 missing time to discharge were included as censored 1 hour post-randomization.
 432 ^{c.} Ordinal composite outcome with patients who died on or before day 30 assigned the worst possible score of –1. Surviving patients were ranked according
 433 to the number of calendar days on which any respiratory, cardiovascular or renal support was received at any time during that day, starting from day 1 (the
 434 day of randomization) up to and including day 30. Following rows show individual components: 30-day mortality and days free from organ support at 30
 435 days among survivors.
 436

ACKNOWLEDGEMENTS

Funding

This trial was funded by the UK National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (project number: NIHR130508). ICNARC was the trial sponsor. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funder and Sponsor had no role in any aspect of the design or conduct of the study, writing of this article or the decision to submit the manuscript for publication. This research was conducted during the tenure of a Health Research Council of New Zealand Clinical Practitioner Fellowship held by PY and NIHR Pre-doctoral Fellowship in Epidemiology (NIHR302788) held by WNC.

Authors' affiliations

¹Peninsula Medical School, University of Plymouth, Plymouth, UK; ²Intensive Care Unit, University Hospitals Plymouth NHS Trust, Plymouth, UK; ³Clinical Trials Unit, Intensive Care National Audit & Research Centre (ICNARC), Napier House, London, UK; ⁴Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK; ⁵Critical Care, Maidstone and Tunbridge Wells NHS Foundation Trust, Kent, UK; ⁶Patient and Public Representative, Bristol, UK; ⁷Perioperative and Critical Care Theme, NIHR Southampton Biomedical Research Centre, University Hospital Southampton/University of Southampton, Southampton, UK; ⁸Medical Research Institute of New Zealand, Wellington, New Zealand; ⁹Respiratory Medicine, Northern Care Alliance NHS Foundation Trust, Salford Royal University Hospital, Salford, UK; ¹⁰Integrated Critical Care Unit, South Tyneside and Sunderland NHS Foundation Trust, Sunderland, UK; ¹¹Critical Care, Aneurin Bevan University Health Board, Cwmbran, UK; ¹²Critical Care, Queen Mary's University London, UK; ¹³Adult Critical Care Unit, St Bartholomew's Hospital, London, UK; ¹⁴Intensive Care Unit, Wellington Hospital, Wellington, New Zealand; ¹⁵Australian and New Zealand

Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia;

¹⁶Department of Critical Care, University of Melbourne, Melbourne, VIC, Australia.

Authors' contributions

JD and DH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. DM, MG, KR and PM conceived and led the design of the trial. Management, including acquisition of data, was led by TS with support from DG, JC, WC, LL, ARB, AFJ. JD, AC, ZS, WC, AW, DH led and delivered the analysis. RG provided input from a former patient. DM, MD, MG, JJ, ROD, AR, TS, PY provided clinical input and oversight. All authors contributed to interpretation of the data and critically reviewed the manuscript. DM and PM wrote the first draft of the manuscript.

Disclosures

DM is Editor in Chief of the Journal of the Intensive Care society and has received NIHR funding: 135577, 135577 and 129318. MG is in part funded by the NIHR Southampton Biomedical Research Centre and in part funded by the NIHR Senior Investigator Scheme. MG has served on the medical advisory board of Edwards Lifesciences Ltd and received honoraria and unrestricted study funding from Edwards Lifesciences Ltd. TS has received speaker fees from Thermofisher Ltd, and from Biotest AG. TS is Editor-in-Chief for Critical Care Explorations, Trustee for the Intensive Care National Audit and Research Centre and has received the following NIHR funding: 131784, 132254. KR is Director of the NIHR Health and Social Care Delivery Research Programme. DH is a member of the NIHR Health Technology Assessment programme general funding committee.

Data sharing

A data sharing statement provided by the authors is available with the full text of this article in Supplement 3.

486 Group information

487 *Chief investigator and co-investigators:* Daniel Martin, PhD (Chief Investigator); Paul
488 Mouncey, MSc (co-Lead Investigator); Miriam Davey, PGDip; James Doidge, PhD; Roger
489 Garrett, PhD; Doug Gould, PhD; Michael Grocott, MD; David Harrison, PhD; Joanne Jones,
490 RN; Ronan O’Driscoll, MD; Alvin Richards-Belle, BSc; Kathryn Rowan, PhD; Zia Sadique,
491 PhD; and Paul Young, PhD.

492 *Trial Steering Committee:* Tim Walsh, MD (Chair, independent); Felix Achana, PhD
493 (independent); Jeremy Dearling (independent); Kathryn Puxty, MD (independent); Anthony
494 Gordon, MD (independent); Sarah Vollam, PhD (independent); Daniel Martin, PhD (non-
495 independent); and Paul Mouncey, MSc (non-independent).

496 *Data Monitoring and Ethics Committee:* John Norrie, PhD (Chair); Anders Perner, PhD; and
497 Todd Rice, MD.

498 *Trial Management Group:* Daniel Martin, PhD; Paul Mouncey, MSc; Doug Gould, PhD;
499 Tasnin Shahid, BSc; James Doidge, PhD; Zia Sadique, PhD; Miriam Davey, PGDip; Roger
500 M Garrett, PhD; Michael Grocott, MD; Joanne Jones, RN; Diane Mackle, PhD; B Ronan
501 O’Driscoll, MD; Alvin Richards-Belle, BSc; Anthony Rostron, PhD; Tamas Szakmany, PhD;
502 Paul Young, PhD; Kathryn Rowan, PhD; and David Harrison, PhD.

503 Additional clinical trials unit contributors

504 Hannah Chester, Hannah Sedgwick, Millie Parke, Naomi Lau, Carly Au, Alexina Mason,
505 Lorna Miller

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