Mega ROX overarching statistical analysis plan

Trial: Mega randomized registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX)

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Section 1 Administrative Information

Title

Mega randomized registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX)

Trial registration

Prospectively registered (Mega-ROX Australian and New Zealand Clinical Trials Registry number, ACTRN 12620000391976)

SAP version

Version 2.0 | 9 November 2026

Finalized blinded to study data prior to database lock.

Online posting date: 10 November 2026

Posting location: https://www.doi.wellingtonicu.com/

Protocol version

This document has been written based on information in the Mega-ROX study protocol and statistical analysis plan:

> Young PJ, Arabi YM, Bagshaw SM, et al. Protocol and statistical analysis plan for the mega randomized registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX). Critical Care and Resuscitation. 2022;24:137–149. doi:10.51893/2022.2.OA4 [1].

Names and affiliations

Document prepared by Professor Jessica Kasza, Monash University; and Professor Paul Young, Intensive Care Unit, Wellington Hospital

Signatures:

Signature of senior statistician Prof Jessica Kasza: _  *Date: 9 November 2026*

Signature of chief investigator Prof Paul Young: _  *Date: 9 November 2026*

Section 2 Introduction

Brief background and rationale

The published protocol provides the detailed background to this trial:

Young PJ, Arabi YM, Bagshaw SM, et al. Protocol and statistical analysis plan for the mega randomized registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX). Critical Care and Resuscitation. 2022;24:137–149. doi:10.51893/2022.2.OA4 [1].

Objectives

Research hypothesis:

We hypothesize that among adult ICU patients who receive unplanned invasive mechanical ventilation, conservative oxygen therapy reduces in-hospital all-cause mortality up to 90 days from the date of randomization when compared with liberal oxygen therapy.

Study objective:

To determine whether conservative oxygen therapy, compared to liberal oxygen therapy, reduces in-hospital all-cause mortality up to 90 days from the date of randomization.

Section 3 Trial Methods

Trial design

Investigator-initiated, two parallel arm, superiority individually-randomized controlled trial (RCT).

Randomization

Treatment assignment was performed using a secure, centralized, web-based, randomization interface. Participants were enrolled in the study by ICU doctors, nurses, and research staff. The assigned intervention was communicated to the bedside nurse who implemented the study intervention. One novel feature of the Mega-ROX trial is the use of adaptive randomization to increase the probability that trial participants are allocated to the oxygen regimen that appears to be associated with the lowest in-hospital mortality risk for their condition based on available data from interim analyses. The conditions of interest are suspected hypoxic ischemic encephalopathy following resuscitation from cardiac arrest, sepsis, and acute brain injury or condition other than hypoxic ischemic encephalopathy. Patients with none of these conditions were included in a fourth group. If ICU clinical staff were enrolling a patient who fit into more than one of the first three groups, they were assigned to one group for the purposes of allocating study treatment during randomization. This was achieved by using a hierarchy determined by the magnitude of the absolute risk difference between observed treatment groups for that subgroup. This approach is based on the rationale that a larger risk difference corresponds to a smaller number needed to treat.

At the beginning of the trial, participants within each group were preferentially randomized, in a ratio of 1.05:1, to the oxygen regimen that was associated with the lowest in-hospital mortality risk for that particular patient group in ICU-ROX; details in the Mega-ROX protocol [1]. After the first interim analysis, randomization ratios for each patient group were not known by the study management committee or the investigators. Computer-generated random numbers were used to determine the sequence. No stratification or permuted block randomization was used, and the randomization sequence was concealed from clinical staff, the management committee, and the investigators.

Details on the randomization ratios that applied for individual patients will be provided in the Supplementary Methods file accompanying the trial manuscript.

Sample size

Assuming mortality of 29.7% in the liberal-oxygen group, 38,420 participants provides 90% power to detect an absolute mortality difference of 1.5 percentage points at a two-sided alpha of 0.05. The planned sample was increased to 40,000 for losses to follow-up, consent withdrawal and the small inefficiency from adaptive allocation. A website error prevented automatic closure at 40,000; the retained trial cohort comprises 40,003 unique participants.

Framework

This trial uses a superiority hypothesis-testing framework for the primary outcome. Results will be reported in accordance with CONSORT 2025 [2].

Statistical interim analyses and stopping guidance

Interim efficacy and safety analyses were conducted after 1000, 8000, 16,000, 24,000 and 32,000 patients were enrolled, using registry data for the primary outcome that were available when each enrollment threshold was passed. The primary purpose of the initial interim analysis was to monitor the recruitment rate, with a secondary purpose to update randomization ratios. A model for the outcome including an interaction term between treatment group and subgroup was fit, with estimates of the relative risk in each subgroup obtained, adjusting for site. For each subgroup, the randomization ratio was set to 1:1 if the relative risk was between 0.9 and 1.1, and set to 1.05:1 otherwise, favoring the group with the lower risk of deaths. At subsequent interim analyses, a Haybittle–Peto symmetric stopping boundary of $P < 0.001$ was applied (preserving the overall alpha of 0.05). Mega-ROX was not stopped at an interim analysis.

Timing of final analysis

The final analysis will use the completed 90-day follow-up of all 40,003 unique participants. Analysis code will be developed using dummy treatment labels where feasible. The dates of SAP approval, public posting, database lock and access to treatment results will be recorded.

A total of 40,003 unique participants is confirmed. Only the first allocation will be used for any participant randomized more than once in the intention-to-treat analysis.

Timing of outcome assessments

The primary outcome was measured at 90 days after randomization.

Section 4 Statistical Principles

Level of statistical significance

For the primary outcome comparison and unless otherwise stated applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

The Holm–Bonferroni method will control the family-wise error rate at 5%. The family includes six outcomes if ANZ all-cause day-90 mortality can be reported with the primary manuscript under the linkage requirement in Section 6. If reporting is deferred, the family comprises the other five outcomes. Any later report of ANZ all-cause day-90 mortality will present the comparison separately without a Holm-adjusted P value. Section 6 identifies one formal test per outcome. Supporting analyses, including sensitivity analyses of the primary outcome, are outside this family.

For a family of m outcomes, order the P values from smallest to largest. Reject the kth null hypothesis if its ordered P value is at most $0.05/(m - k + 1)$, stopping at the first non-rejection. Multiply the ordered P values by $m, m - 1, \ldots, 1$, respectively. Each adjusted P value is the maximum of the products through that rank, capped at 1. Raw and adjusted P values will be reported for estimable comparisons. Ordinary 95% confidence intervals are pointwise and are not multiplicity-adjusted.

A comparison in the applicable family that does not yield a valid P value, including failure of a model-based test to produce the required treatment-effect estimate or standard error, will remain in that family, with P=1 used solely for multiplicity adjustment. The comparison will be reported as not estimable. Failure of a supporting effect-estimation model will not replace an available pre-specified formal test. In particular, failure of a supporting Cox model will not invalidate an available formal log-rank test.

Confidence intervals to be reported

All confidence intervals will be two-sided 95% confidence intervals.

Adherence and protocol deviations

The details of the oxygen therapy regimens that were used have been outlined in the protocol manuscript for the overarching Mega-ROX trial program [1]. In brief, for patients allocated to conservative oxygen therapy, the lowest possible fraction of inspired oxygen (FIO_2) to achieve an arterial oxygen saturation on pulse oximetry (SpO_2) of ≥91% was used. In this group, the protocol states that SpO_2 levels of greater than 94% were to be strictly avoided and an upper SpO_2 alarm limit of 95% was to be used whenever supplemental oxygen was being administered in the ICU to minimize the risk of exceeding the upper SpO_2 limit. For patients allocated to liberal oxygen therapy, oxygen was delivered as directed by the treating clinician with the caveat that the minimum FIO_2 allowed while the patient is invasively mechanically ventilated will be 0.30. The duration of study therapy was until ICU discharge or 90 days, whichever was sooner. The study intervention was applied in the ICU only. If patients were readmitted to ICU during their index hospital admission, they recommenced the study treatment to which they were randomized. If, during the course of their ICU admission, patients were transported outside of the ICU for procedures, they received standard (non-study) treatment. Similarly, if an increase in FIO_2 was required for procedures performed in the ICU including (but not limited to) bronchoscopy, suctioning, tracheostomy, or preparation for extubation, it was permitted in both groups. There were no restrictions to concomitant treatments provided to patients.

Patients with protocol deviations will be included in the intention-to-treat analysis (i.e. the intercurrent event of protocol deviations will be handled using the treatment policy approach). The number of patients with deviations will be reported and, where collected, episodes and reasons will be reported by randomized

allocation. Permitted temporary changes for transport or procedures are not protocol deviations and were not specifically recorded. Patients may have more than one type of protocol deviation, so percentages need not sum to 100%.

Receipt of the allocated strategy

Receipt requires purposeful implementation of the allocated oxygen-management strategy at some point. Oxygen values that happen to resemble that strategy do not by themselves establish receipt. Allocation never communicated, or a strategy withheld throughout the ICU admission, is classified as never received. Initial withholding followed by purposeful implementation counts as receipt. Eligibility deviations and treatment receipt are assessed separately; never being invasively ventilated does not by itself establish non-receipt.

Participant oxygen exposure summaries

Median percentages and recorded hours of SpO_2 ≥97%, SpO_2 <88%, and FIO_2 0.21 (room air), as defined in Table S3, will be compared using quantile regression with robust standard errors clustered by site. Comparisons of the binary outcomes of at least one PaO_2 <60 mmHg or >100 mmHg will use log-binomial models with a log link accounting for site by including random intercepts for site. Denominators, numbers of events, risk ratios and corresponding 95% confidence intervals will be reported. These exposure comparisons are outside the secondary Holm–Bonferroni family.

Daily oxygen measurements

Each participant's daily mean oxygen measurements will be calculated from available scheduled readings, without filling missing times. PaO_2 will be reported in mmHg and FIO_2 as a fraction. Group means (with each individual patient equally weighted) and standard errors will be plotted at CRF days 0–7, with contributing participant counts provided for every day, allocation and plotted measure.

The number of participants contributing daily mean oxygen measurements will be reported by randomized allocation and measure. Later-day comparisons condition on remaining observable; achieved oxygen exposure may differ from the assigned strategy and is not itself randomized.

Analysis populations and estimand

Except where stated otherwise, analyses follow intention to treat: each unique participant is included according to the first randomized allocation when use of study data is permitted. Treatment cessation, ineligibility, crossover and non-receipt do not remove participants. Withdrawal of treatment alone does not withdraw permission to use data. Diagnostic adjustment and subgroup analyses will use the final HIE, sepsis and non-HIE brain-condition categories, except for the primary-outcome sensitivity analysis using the originally selected stratification variables described in Section 6. Misclassification counts will be reported in the overarching trial; further analyses of diagnostic reclassification or misclassification will be addressed within the respective nested trials. The primary estimand of interest is described in the table below.

<table>
<tr><td colspan="2">Objective: To determine whether conservative oxygen therapy, compared to liberal oxygen therapy, decreases the risk of in-hospital all-cause mortality up to 90 days from the date of randomization.</td></tr>
<tr><td colspan="2">Estimand: Relative risk of incidence of in-hospital all-cause mortality up to 90 days from the date of randomization among adult ICU patients who receive unplanned invasive mechanical ventilation, assigned to conservative oxygen therapy, relative to liberal oxygen therapy.</td></tr>
<tr><td colspan="2">Treatment:
Conservative oxygen therapy: This is described in full in the protocol, briefly, FIO_2 decreased to a minimum of 0.21 (room air) as rapidly as possible, provided that SpO_2 is greater than the default acceptable lower limit of 91%.
Liberal oxygen therapy: Described in full in the protocol, but briefly, minimum acceptable FIO_2 during mechanical ventilation in an ICU will be 0.30.</td></tr>
<tr><td>ESTIMAND</td><td>ANALYSIS</td></tr>
<tr><td>Target population: adult patients in the ICU who receive unplanned invasive mechanical ventilation.</td><td>Analysis set: All randomized participants, except those for whom consent for the use of study data is withdrawn. Patients assigned to receive conservative oxygen therapy through randomization will be the treatment group, patients assigned to receive liberal</td></tr>
</table>

	oxygen therapy the comparator group. Only the first randomization of any patients included multiple times will be used.
Variable: in-hospital all-cause mortality up to 90 days from the date of randomization.	**Outcome measure**: In-hospital mortality. Patients who survive the index hospital admission and are discharged within 90 days will be defined as alive.
Handling of intercurrent events: - Treatment as randomized not received: patients included in their randomized groups (treatment policy strategy). This applies to any deviations from the randomized treatment. - Patient discharge not medically indicated: patients will be defined as alive if discharged from the hospital even if it is not medically indicated (treatment policy strategy).	**Handling of missing data:** The primary analysis will use observed primary outcomes. Best–worst and worst–best analyses will be performed whenever primary outcomes are missing. Multiple imputation with 20 datasets will be performed if either extreme scenario changes the conclusion of the primary comparison at the two-sided 5% significance level. The detailed approach is described below. **Supplementary analysis**: The analysis of the primary outcome will be repeated as follows: 1. Eligible patients only. Some patients who were not eligible for the study were inadvertently randomized; an analysis of the primary outcome excluding these ineligible patients will be conducted. 2. Eligible patients who received their randomized treatment only. In addition to excluding ineligible patients, eligible patients who never received their randomized treatment will be excluded in this analysis. Sensitivity to stratification variable misclassification: the primary-outcome analysis will be repeated using the originally selected HIE, non-HIE brain-condition and sepsis values rather than their final recorded values, with risk ratios and risk differences estimated as described in Section 6. 3. Hypothetical strategies to handle non-medically-indicated patient discharge: a. Patients will be defined as dead if assigned to the conservative oxygen strategy and alive otherwise. b. Patients will be defined as alive if assigned to the conservative oxygen strategy and dead otherwise.
Population-level summary measure: Relative risk and risk difference of in-hospital all-cause mortality up to 90 days from the date of randomization comparing conservative and liberal oxygen therapy groups.	**Analysis approach**: The relative risk will be estimated using a log-binomial model adjusted for the final recorded presence/absence of each of suspected hypoxic ischemic encephalopathy following resuscitation from a cardiac arrest, sepsis, and acute brain injury or condition other than hypoxic ischemic encephalopathy at randomization. Random effects for site will be included. The risk difference will be estimated by fitting a model that is identical except for the link function: an identity link will be used.

Section 5 Trial Population

Screening data

Screening data were collected and a CONSORT flow diagram will be used to summarize these data.

Eligibility

Trial inclusion criteria are described in the trial protocol [1]. Reasons for exclusion will be summarized in the CONSORT flow diagram.

Recruitment

A CONSORT flow diagram will be used to describe the number of people consented to participate, randomized, allocated to each treatment group, those lost to follow-up (including reasons) and analyzed [2].

Withdrawal and follow-up

If a participant withdrew from the study, any data provided up to the point of withdrawal will be analyzed in accordance with the principle of intention to treat, whereby data from all randomized individuals is included in analyses, unless the participant specifically requests to withdraw their data from the study. Losses to follow-up will be summarized in the CONSORT flow diagram by treatment group.

Data sources and ascertainment populations

The study database will be used for variables collected in both the study database and a registry. Variables collected only in a registry or only in the CRF will be taken from that source. Table S1 describes the sources and availability of data.

Sites in Canada used both CRF and registry routes for collection of data; the first 34 CA001 participants used REDCap. SA002, a site in Saudi Arabia, used REDCap for additional fields. In Brazil, hospital outcome data could be recorded in both the main study database and REDCap for the same participants.

Each analysis will include participants at sites and during periods in which the relevant outcome was collected. Primary mortality, index-hospital survival, and ICU and hospital discharge will be analyzed across all jurisdictions. Ventilation and discharge-destination data were collected at all sites except SA001; SA002 is included. Both named sites are in Saudi Arabia. Post-discharge day-90 mortality is recorded through registry pathways in ANZ, India, Malaysia, Nepal and Pakistan (Table S1). The pre-specified formal day-90 mortality analysis will use the ANZ registry population eligible for that pathway, with linkage success reported separately.

The number of patients in jurisdictions/sites that collected each variable will be reported, as will the number of patients with observed data. Reasons for exclusions will be reported. Known binary outcomes will be included even when exact event times are missing. Appendix tables will report the jurisdiction map and data completeness.

Baseline descriptive measures

The Appendix contains the planned tables.

Baseline characteristics will be summarized as appropriate (means and standard deviations for continuous variables that appear to be distributed approximately symmetrically, medians and interquartile ranges for other continuous variables, counts and percentages for categorical variables). Tests of statistical significance will not be undertaken for comparing baseline characteristics of treatment groups; rather the clinical importance of any imbalance will be noted.

Baseline oxygenation uses the last arterial blood gas before randomization and its paired FIO_2. If no gas was obtained, the last pre-randomization FIO_2 alone cannot supply a PaO_2/FIO_2 ratio. Baseline PaO_2 will be reported in mmHg; post-randomization oxygen measurements will not be used as baseline measurements.

Mega-ROX participants receive unplanned invasive mechanical ventilation. ICNARC coding classifies patients as surgical or non-surgical/medical; admission source is recorded separately (Table S1). Brazil collected SAPS 3, not APACHE II. APACHE II will be reported descriptively where collected and will not be included in adjustment models. SAPS 3 remains descriptive and is not substituted for APACHE II.

Diagnostic categories used in randomization

HIE, sepsis and other acute brain conditions governed the adaptive randomization probabilities. Some patients were incorrectly classified as either having or not having these conditions at baseline; their

randomization was based on their initial classification. The primary and subgroup analyses will use the final recorded diagnostic categories [3]. The number and percentage of participants with misclassified stratification variables will be reported by randomized allocation, overall and separately for HIE, non-HIE brain conditions and sepsis (Table S6). Misclassification will be defined as a difference between the originally selected and final recorded presence/absence values. The primary-outcome sensitivity analysis using the originally selected values is described in Section 6. Further diagnostic-reclassification analyses will be reported in the respective nested trial manuscripts.

Representativeness

Representativeness will compare ANZ trial participants with other ANZICS Adult Patient Database admissions at the same participating ICUs during their recruitment periods. The comparison will use unplanned invasive ventilation and other eligibility criteria observable in both data sources. Counts and characteristics available and defined comparably in both sources will be summarized; trial eligibility will not be inferred from criteria absent from the registry. These comparisons describe representativeness within this ANZ registry population (Table S7); similar comparisons with other registries will be reported if feasible.

Section 6 Analysis

Outcome definitions

Outcome	Definition	Population	Principal estimate or test
Primary in-hospital mortality	Death in the index hospital on or before day 90; verified live discharge or survival in hospital at day 90 is a non-event.	Full overarching population	Random-site-intercept log-binomial risk-ratio; separate identity-link to obtain risk difference.
Index-hospital survival	From randomization to in-hospital death; end follow-up at live discharge/transfer, day 90 or last reliable in-hospital observation.	Full population with usable timing	Log-rank test.
Live ICU discharge	First live exit from index ICU; death before exit is a competing risk. Follow to day 90.	Full population with usable timing	Treatment-effect test from a Fine–Gray model adjusted for sepsis, HIE and non-HIE brain conditions, with death as a competing risk.
Live hospital discharge	First live exit from index hospital; death before exit is a competing risk. Follow to day 90.	Full population with usable timing	Treatment-effect test from a Fine–Gray model adjusted for sepsis, HIE and non-HIE brain conditions, with death as a competing risk.
Total invasive ventilation hours	Completed total during the index ICU episode, potentially including pre-randomization hours and hours before death.	Collection population excluding SA001	Diagnosis-adjusted quantile regression with robust standard errors accounting for clustering by site.
Direct discharge home	Live direct discharge from index hospital to home by day 90. Death, transfer elsewhere or continuing admission is counted as not being discharged home.	Destination collection population excluding SA001	Random-site-intercept binary risk-ratio model.

Outcome	Definition	Population	Principal estimate or test
All-cause day-90 mortality	Death by day 90, including after hospital discharge; reliable survival through day 90 establishes survival.	Predefined ANZ registry coverage population	Random-site-intercept binary risk-ratio model.

Analysis methods

Primary outcome and time origins

The index ICU admission is the episode during which a patient was randomized. The index hospital admission is the hospital episode during which a patient was randomized; documented live discharge or transfer out ends that episode. Later readmission does not extend it. Time zero for the 90-day windows and event-time analyses is randomization. Verified death within the index hospital by day 90 is the primary event, regardless of whether its exact timestamp is available.

Recorded event dates and times will be used. For ICU or hospital discharge with a known date but missing time, midday will be the assumed time of discharge. The number of participants for whom the midday convention is used will be reported.

Primary outcome and binary secondary outcomes

For the primary analysis of binary outcomes, risk ratios will be estimated using log-binomial models adjusted for the final presence or absence of suspected HIE following cardiac arrest, sepsis, and other acute brain injury or condition. A random intercept for site will be included. Risk differences will be estimated using a separate binomial model with the same covariates and random site intercept but an identity link. The number of observed events, denominators, group proportions, risk ratios, risk differences and 95% confidence intervals will be reported. Ratios compare conservative with liberal oxygen; risk differences are conservative minus liberal, in percentage points. The primary P value is the one corresponding to the estimate of the risk ratio.

Model convergence

If the initially specified model does not converge in a complete-case analysis, the estimate and confidence interval from the first convergent model in the following sequence will be reported: (1) the model will be fitted with site-clustered robust standard errors instead of a random site intercept; (2) sites with fewer than 10 participants will be combined and the original model refitted; (3) sites with fewer than 20 participants will be combined and the original model refitted; (4) the random-site-intercept model will be refitted, omitting diagnostic covariates in the following order: HIE alone; non-HIE brain conditions alone; sepsis alone; HIE plus non-HIE brain conditions; HIE plus sepsis; sepsis plus non-HIE brain conditions; then all three diagnostic terms.

This sequence will be applied separately to the log-link and identity-link models, retaining the link appropriate to each estimand and reporting the actual model used. If the pre-specified sequence does not provide an estimate of the treatment effect, we will report that estimate is unavailable rather than introducing an unplanned alternative estimator.

The primary analysis of the primary outcome will be repeated in eligible participants only and in eligible participants who received their allocated strategy. In addition, the non-medically-indicated-discharge scenarios below will be applied. These supporting populations do not replace the intention-to-treat comparison. Eligibility and purposeful receipt are classified separately from observed oxygen values.

Survival time

Survival time during the index hospitalization will be displayed using Kaplan–Meier curves and groups compared using a two-sided log-rank test. An unadjusted Cox model with treatment alone and a second Cox model including treatment and the three final diagnostic indicators, with site-clustered robust standard errors will be fit. The log-rank test is the formal survival comparison that will be considered in the Holm-Bonferroni method; Cox hazard ratios and their 95% confidence intervals are supporting effect estimates. Failure of a supporting Cox model will not invalidate an available formal log-rank test.

Survival follow-up ends at in-hospital death, live discharge or transfer out of the index hospital, day 90, or last reliable in-hospital observation. Post-discharge deaths will not be included in the all-site analysis because their ascertainment differs by jurisdiction. The Kaplan-Meier curve will be labeled “Survival during the index hospitalization”; it is not 90-day all-cause survival. The separate ANZ all-cause survival display is subject to the linkage requirement below.

The small-site pooling sequence as specified for binary outcomes will apply to survival models if needed: sites with fewer than 10 participants, then fewer than 20, will be combined and the model refitted. The proportional hazards assumption will be assessed using Schoenfeld residuals. Departures from the assumption of proportional hazards will be noted but no other models will be fit.

Live ICU and hospital discharge

For ICU discharge, the event is the first live exit from the index ICU after randomization, including transfer to another ICU; death before that exit is a competing risk. Later readmission or death after discharge is irrelevant. For hospital discharge, the event is live exit from the index hospital and death before exit is a competing risk. Follow-up ends at day 90 or the last reliable observation; ongoing admission at day 90 is administratively censored.

Fine and Gray subdistribution-hazard regression models with treatment and the three final diagnostic indicators will be fit, using site-clustered robust standard errors. The small-site pooling sequence as specified for binary outcomes will apply to these models if needed: sites with fewer than 10 participants, then fewer than 20, will be combined and the model refitted. Cumulative incidence functions for live discharge and competing death will be displayed. The P value associated with each Fine and Gray treatment comparison is the formal comparison for its respective outcome to be considered when the Holm-Bonferroni method is applied. Subdistribution hazard ratios and 95% confidence intervals will be reported; a ratio above 1 indicates greater cumulative incidence of live discharge. A median time to live ICU or hospital discharge with its 95% confidence interval will be reported only if the estimated cumulative incidence of the corresponding live discharge reaches 50%; otherwise it will be reported as not reached.

Recorded durations and ventilation

The available ventilation measure is completed total invasive ventilation hours during the index ICU episode. It can include ventilation before randomization and hours accrued before death. An extubation or liberation date will not be inferred from this total, nor will ICU-admission-to-randomization time be subtracted. Total ventilation hours will be compared between groups using quantile regression with treatment and the three final diagnostic indicators and site-clustered standard errors, using the qreg2 command in Stata. The treatment coefficient is a conditional median difference in hours, conservative minus liberal. This supplies the formal ventilation P value for the application of the Holm-Bonferroni method.

Quantile-regression comparisons of ICU and hospital durations will be performed as supporting analyses of observed completed episode lengths, adjusting for treatment and the three final diagnostic indicators with site-clustered standard errors. Each duration will be measured from randomization time to the recorded end of the index episode or to time of death when applicable, using all available index-episode follow-up, including beyond day 90. Ongoing ICU or hospital episodes at the last available follow-up will be right-censored at that time; their censored elapsed times will not be treated as completed durations in quantile or log-linear regression. Completed, right-censored and missing completed-duration counts and available follow-up will be reported by allocation. The number of patients who survive and die prior to discharge will be reported. These resource-use summaries are distinct from the censored time to live discharge.

Log-linear regression models for positive completed total ventilation hours and ICU and hospital durations will be fit, adjusted for the three diagnostic indicators with site-clustered robust standard errors. The exponential of the treatment coefficient will be taken to report a conservative-to-liberal ratio of geometric means. Observed medians and quartiles, geometric means and 95% confidence intervals, and descriptive summaries will be reported by survival status (survival to the end of the relevant episode); for ventilation strata, survival will be to ICU discharge. Survivor-restricted comparisons are descriptive post-randomization summaries.

Zero ventilation hours will remain in the quantile analysis and will be counted separately; geometric means will be reported for participants with positive durations. Patients with durations of length zero will be excluded from the log-linear regression models.

Direct discharge home and ANZ day-90 mortality

Discharge home is live discharge directly from the index hospital to home by day 90. Death, transfer to another medical facility or another destination, and continuing admission at day 90 are non-successes. A missing destination after live discharge will result in a missing value for this outcome. The analysis approach outlined for the primary outcome and binary secondary outcome will be applied, excluding site ID SA001 and retaining site ID SA002.

All-cause mortality by day 90 includes deaths after discharge and uses the predefined ANZ registry-coverage population. The analysis approach outlined for the primary outcome and binary secondary outcome will be applied. The number of patients eligible for the ANZICS APD and the number with registry data will be reported. Absence of a death recorded in the linked registry establishes survival only where coverage and linkage support that conclusion; live hospital discharge alone does not establish day-90 survival. No day-90 all-cause outcome will be imputed in jurisdictions where it was not collected. Day-90 all-cause mortality, including deaths after hospital discharge, will be reported in the primary manuscript only if death registry linkage to the ANZICS Adult Patient Database (APD) covers dates beyond the final Mega-ROX trial participant's day-90 follow-up. Otherwise, reporting of this outcome will be deferred.

Eligibility for the ANZ day-90 registry analysis will be determined by participating site, recruitment period and the applicable registry coverage and residency requirements, independently of linkage success. Eligible participants whose day-90 vital status cannot be established will have a missing outcome; they will remain in the reported eligible denominator. Registry linkage success and outcome completeness will be reported separately.

Secondary comparisons and multiplicity

The five outcomes are index-hospital survival (log-rank test), live ICU discharge and live hospital discharge (Fine–Gray treatment tests), total invasive ventilation hours (quantile-regression treatment test) and direct discharge home (log-binomial treatment test). The log-binomial treatment test for ANZ all-cause day-90 mortality is the sixth comparison when included. Section 4 specifies the Holm–Bonferroni procedure for the applicable family. The additional Cox, quantile and geometric-mean models are supporting analyses.

Additional covariate adjustment

For the primary outcome, an additional analysis including terms for patient age and sex will be fit, with a risk ratio and risk difference estimated. This will be followed by models also including baseline covariates with clinically meaningful imbalances between allocations. APACHE II and SAPS 3 will not be included in these adjustment models due to the fact that these may not be pre-randomization variables.

The baseline covariates included because of clinically meaningful imbalances will be selected from summaries with treatment allocation masked, before treatment-effect results are examined. The selected covariates and the clinical rationale for their inclusion will be documented in the analysis record.

If these models fail, the approach outlined for the primary analysis will be applied, with omission of additional covariates one at a time in this order: imbalanced baseline variables, age, then sex. If required, pairs of variables will be omitted using the order above, e.g. (#1, #2), (#1, #3), …, (#k-1, #k).

Sensitivity to stratification variable misclassification

As a sensitivity analysis, the primary outcome will be analyzed as specified for the primary analysis, replacing the final recorded HIE, non-HIE brain-condition and sepsis indicators with the originally selected values recorded at randomization. Risk ratios and risk differences and their 95% confidence intervals will be estimated using the same log-link and identity-link binomial models, respectively, with the same site effect. The alternative analysis approaches specified under Model convergence will be applied separately to each model if required, using the originally selected diagnostic variables throughout. The outcome definition, intention-to-treat population and treatment-effect direction will otherwise be as specified for the primary analysis. The number and percentage of participants with misclassified stratification variables will be reported by randomized allocation as described in Section 5 and Table S6.

Sensitivity to bias induced by response-adaptive randomization

In the analysis of the primary outcome, inverse probability of treatment weighting will be applied to assess sensitivity to bias induced by response-adaptive randomization [4]. Each participant will receive a weight equal to the inverse of the probability of receiving their allocated treatment that applied to that participant at randomization. Categorical terms for randomization epoch will be included to allow for population drift over

time [4]. Epochs will be defined by the dates on which updated randomization probabilities were implemented.

Subgroup analyses

Subgroup analyses of the primary outcome will be conducted for the following subgroup pairs:

i) Suspected hypoxic ischemic encephalopathy following resuscitation from cardiac arrest vs not;

ii) Sepsis vs not;

iii) Acute brain injury or condition other than hypoxic ischemic encephalopathy vs not;

iv) Confirmed or clinically suspected COVID-19 vs not;

v) Recruited in a high income country vs a low or middle income country;

vi) Time from ICU admission to randomization less than 2 hours vs greater than or equal to 2 hours.

Models for these analyses will be as described in the primary analysis for the primary outcome, including terms for the subgroup indicator and interactions between the subgroup and randomized group. Treatment effects in each subgroup and interaction P values will be reported. These exploratory interaction tests will not be included in the Holm–Bonferroni adjustment for the applicable secondary family.

The time from ICU admission to randomization subgroup analysis will include only those patients with ICU admission time recorded. These admission times will be drawn from registry data where available.

Country income will use the World Bank fiscal year 2027 classification, fixed for all participants [5]. Australia, New Zealand, Canada, Ireland, Italy, Japan, Kuwait, Oman and Saudi Arabia will form the high-income group; Brazil, India, Malaysia, Nepal and Pakistan will form the low- or middle-income group.

Missing data

The primary analysis will use participants with observed primary outcomes. If any primary outcomes are missing, best–worst and worst–best analyses will be performed. In the worst-best imputation, the worst outcome event (i.e., in-hospital death within 90 days) is assigned to all patients missing the outcome in one treatment group, and the best outcome event (i.e., no in-hospital death within 90 days, including survival in hospital at day 90) is assigned to all patients missing the outcome in the other treatment group. The best-worst scenario is the exact opposite assignment of outcomes. If either extreme scenario changes the conclusion of the primary comparison at the two-sided 5% significance level, multiple imputation with 20 datasets will also be performed. A change in conclusion means that the primary treatment test changes between $P < 0.05$ and $P \geq 0.05$, or that the statistically significant result favors the opposite treatment. Results for complete-case and multiply imputed data (if necessary) will both be reported. If the primary outcome is complete, no primary-outcome imputation will be performed.

Where available and suitable, imputed datasets generated under this overarching SAP will be reused in the nested trials. Otherwise, where multiple imputation is required under a nested SAP, missing outcomes will be imputed within the corresponding final diagnostic Yes cohort and its outcome-specific collection population, following that nested SAP.

If multiple imputation is necessary, then any baseline characteristics that will be used in imputation models that have missing values will be imputed using single mean imputation, using center-specific means, or modes for categorical characteristics. Baseline characteristics will be summarized by primary-outcome availability, with t tests or Wilcoxon rank-sum tests for continuous characteristics and chi-squared tests for categorical characteristics to test for differences between patients with and without the primary outcome available. These comparisons will inform the auxiliary variables to be used in multiple imputation (if required), together with the analysis covariates and clinical knowledge. If multiple imputation is required, outcomes will be imputed separately by allocated group including analysis covariates and relevant baseline predictors of outcome or missingness. Imputation models for continuous outcomes will also include terms for site. Imputation models for binary outcomes will not include terms for site due to the possibility of perfect prediction in small sites. Completed total ventilation hours and completed ICU and hospital durations will be imputed jointly using chained equations when imputation of these outcomes is required. Ongoing ICU or hospital episodes right-censored at last follow-up will be distinguished from sporadically missing completed durations; their censored elapsed times will not be substituted or imputed as completed stays using this procedure. No structurally uncollected outcome will be imputed. If required, primary in-hospital mortality will be imputed within the full analysis population. ANZ all-cause mortality up to 90 days will be imputed separately using logistic regression within the ANZ population in which this outcome was collected. Continuous duration outcomes will be imputed using predictive mean matching from the five nearest

neighbors; binary outcomes will be imputed using logistic regression. Imputed datasets will be compared to complete data using density plots for continuous outcomes and plots of proportions for binary outcomes. For analysis of multiply imputed data, the specified convergence sequence will be followed if the selected model fails in more than one quarter of the imputed datasets. The number of datasets fitted and any omissions will be reported, and the available estimates will be combined using Rubin's rules. If the specified convergence sequence does not yield an estimate, the result will be reported as unavailable.

Discharge when ongoing care was medically indicated

The two hypothetical strategies to handle non-medically indicated discharge will be applied, estimating risk ratios and risk differences for the primary outcome. To identify affected patients, the contemporaneous flag for discharge from ICU to home when ongoing care was medically indicated will be used. Verified deaths will be retained as deaths.

Harms

Adverse events were not systematically ascertained. Expected abnormalities and complications of critical illness were not routinely reportable serious adverse events; sites reported events potentially related to the intervention or otherwise of concern [6]. The number of participants affected, serious reports, total reports, recorded relatedness and unresolved reports received under the original trial reporting procedures through database lock will be reported by randomized group. Participant counts and report totals are distinct; these are reported events rather than the incidence of all complications.

Statistical software and illustrative code

Stata version 19 or later or R version 4.4.1 or later will be used. The versions and packages used will be recorded. The following Stata snippets illustrate the planned methods; sepsis, nonHIE and HIE denote the final diagnostic indicators. For the stratification-misclassification sensitivity analysis, these three indicators will be replaced by their originally selected values in both primary-outcome models.

Primary and binary outcomes

```
xi: gllamm outcome i.TreatmentGroup sepsis nonHIE HIE, i(site) fam(binomial) link(log)
xi: gllamm outcome i.TreatmentGroup sepsis nonHIE HIE, i(site) fam(binomial) link(identity)
```

Survival and live discharge

```
stset survival_time, failure(inhospital_death==1)
stcox i.TreatmentGroup, vce(cluster site)
stcox i.TreatmentGroup sepsis nonHIE HIE, vce(cluster site)
stset discharge_time, failure(event_type==1)
stcrreg i.TreatmentGroup sepsis nonHIE HIE, compete(event_type==2) vce(cluster site)
```

Recorded duration models

```
qreg2 recorded_duration i.TreatmentGroup sepsis nonHIE HIE, cluster(site)
reg log_recorded_duration i.TreatmentGroup sepsis nonHIE HIE, vce(cluster site)
```

Code for competing risks models applies only to live ICU or hospital discharge. Log-duration models use positive completed observations and exponentiated treatment coefficients.

Amendments and finalization

Version 2.0 was finalized on 9 November 2026, blinded to study data and prior to database lock. The online posting date is 9 November 2026, with posting to https://www.doi.wellingtonicu.com/. Database-lock and first treatment-results-access dates and the investigator and statistician signatures will be recorded in the study documentation. Amendments will be dated and will state whether they were made before or after access to treatment results.

References

1. Young PJ, Arabi YM, Bagshaw SM, et al. Protocol and statistical analysis plan for the mega randomized registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX). Critical Care and Resuscitation. 2022;24:137–149. doi:10.51893/2022.2.OA4.

2. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomized trials. Nature Medicine. 2025;31:1776–1783. doi:10.1038/s41591-025-03635-5.

3. Yelland LN, Louise J, Kahan BC, Morris TP, Lee KJ, Sullivan TR. Handling misclassified stratification variables in the analysis of randomised trials with continuous outcomes. Statistics in Medicine. 2023;42:3529–3546. doi:10.1002/sim.9818.

4. Lipsky AM, Greenland S. Confounding due to changing background risk in adaptively randomized trials. Clinical Trials. 2011;8:390–397. doi:10.1177/1740774511406950.

5. World Bank. World Bank Country and Lending Groups. Fiscal year 2027 classification. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519. Accessed 29 October 2026.

6. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. CMAJ. 2008;178:1181–1184. doi:10.1503/cmaj.071366.

Appendix planned tables and figures

Table 1: Characteristics of the Patients at Baseline*

Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Body-mass index†	xx.x ± xx	xx.x ± xx
Clinical Frailty Score‡	x (x to x)	x (x to x)
Source of admission to ICU – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)
Median time from hospital admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
SAPS 3 score§	xx.x ± xx	xx.x ± xx
APACHE II score‖	xx.x ± xx	xx.x ± xx
Subgroup diagnoses – no. (%)		
Suspected hypoxic ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Acute brain injuries and conditions (other than ischemic encephalopathy)	xxx (xx.x)	xxx (xx.x)
COVID-19 disease	xxx (xx.x)	xxx (xx.x)
Enrolled in a low or middle income country	xxx (xx.x)	xxx (xx.x)
ICU admission to randomization less than 2 hours	xxx (xx.x)	xxx (xx.x)
Baseline oxygen data		
FIO_2	x.xx ± xx	x.xx ± xx
Median PaO_2 (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median PaO_2/FIO_2 ratio (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are mean ± SD. Variable-specific denominators will be reported; variables not collected at a site will be distinguished from missing observations.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Clinical Frailty Scale scores describe the patient's condition before the current admission and range from 1 (very fit) to 9 (terminally ill).
§ SAPS 3 is reported descriptively for Brazil.
‖ APACHE II is reported descriptively for those countries where it was collected.
Abbreviations: COVID-19, coronavirus disease 2019; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; PaO_2, arterial partial pressure of oxygen; SAPS 3, Simplified Acute Physiology Score 3; APACHE II, Acute Physiology and Chronic Health Evaluation II; SD, standard deviation.

Table 2: Oxygen Exposure Metrics*				
Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)	Between-Group Difference†	Relative risk‡ (95% CI)
Measures of exposure to high arterial oxygen				
Median percentage of hours per patient SpO_2 ≥97% (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median number of hours per patient SpO_2 ≥97% (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
At least one PaO_2 recording >100 mmHg, n (%)	xxx (xx.x)	xxx (xx.x)		x.xx (x.xx to x.xx)
Measures of exposure to low arterial oxygen				
Median percentage of hours per patient SpO_2 <88% (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median number of hours per patient SpO_2 <88% (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
At least one PaO_2 recording <60 mmHg, n (%)	xxx (xx.x)	xxx (xx.x)		x.xx (x.xx to x.xx)
Measures of time spent breathing room air (FIO_2 = 0.21)				
Median percentage of hours per patient FIO_2 = 0.21 (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx(x.xx to x.xx)	
Median number of hours per patient FIO_2 = 0.21 (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	

* Exposure uses CRF days 0–7 after randomization. See Table S3 for matched duration denominators and daily-extreme definitions. Room-air durations include ventilation and the period after extubation. Intervals are not multiplicity-adjusted.
† Median differences were estimated using quantile regression with site-clustered standard errors, as in the restored analysis approach.
‡ Relative risks were calculated using log-binomial models accounting for site. Events and assessable denominators will be reported.

Table 3: Primary and Secondary Outcomes*

	Conservative oxygen (n=XXXX)	Liberal oxygen (n=XXXX)	Estimate (95% CI)
Primary outcome			
Mortality in the index hospitalization within 90 days, n (%)	xxxx (x.xx)	xxxx (x.xx)	Relative risk x.xx (x.xx to x.xx)† Risk difference x.xx (x.xx to x.xx)
Secondary outcomes			
Survival during the index hospitalization through day 90	xxxx events / xxxx patients	xxxx events / xxxx patients	Adjusted Cox hazard ratio x.xx (x.xx to x.xx)
Total hours of invasive ventilation in the index ICU admission			
Number of patients	xxxx	xxxx	
Median (IQR)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Adjusted median difference‡ x.xx (x.xx to x.xx)
Days until discharged alive from ICU			
Number of patients	xxxx	xxxx	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subhazard ratio of time to ICU discharge‡ x.xx (x.xx to x.xx)
Days until discharged alive from hospital			
Number of patients	xxxx	xxxx	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subhazard ratio of time to hospital discharge‡ x.xx (x.xx to x.xx)
Discharged directly home from hospital, n (%)	xxxx (xx.x)	xxxx (xx.x)	Relative risk§ x.xx (x.xx to x.xx) Risk difference x.xx (x.xx to x.xx)
All-cause mortality by day 90 in the ANZ registry population, n (%)	xxxx (xx.x)	xxxx (xx.x)	Relative risk§ x.xx (x.xx to x.xx) Risk difference x.xx (x.xx to x.xx)

* Ordinary secondary 95% confidence intervals are not multiplicity-adjusted. Raw and Holm–Bonferroni-adjusted P values for the applicable secondary family will be reported in this footnote. If ANZ all-cause day-90 mortality reporting is deferred, omit its row and adjust the other five outcomes. Total ventilation hours may include pre-randomization hours and hours before death. Collecting populations exclude SA001 and include SA002 for ventilation and destination; all-cause day-90 mortality is restricted to the ANZ registry population.

† The primary comparison uses a log-binomial model with HIE, sepsis and non-HIE acute brain-condition indicators and a random site intercept. The risk difference uses a separate binomial identity-link model. Ratios compare conservative with liberal oxygen and differences are conservative minus liberal.

‡ Total ventilation hours use diagnosis-adjusted quantile regression with site-clustered standard errors. Live ICU and hospital discharge use diagnosis-adjusted Fine–Gray models with site-clustered standard errors and death competing. Discharge medians and 95% confidence intervals are estimated from the corresponding cumulative incidence function (CIF); if live-discharge incidence does not reach 50%, the median is reported as not reached. They are not medians among observed live discharges.

§ Home discharge and ANZ day-90 all-cause mortality use the same binary-model approach as the primary analysis in their respective collecting populations. The formal survival comparison is log-rank; unadjusted and diagnosis-adjusted Cox hazard ratios are supporting estimates.

Abbreviations: ICU: intensive care unit; IQR: interquartile range.

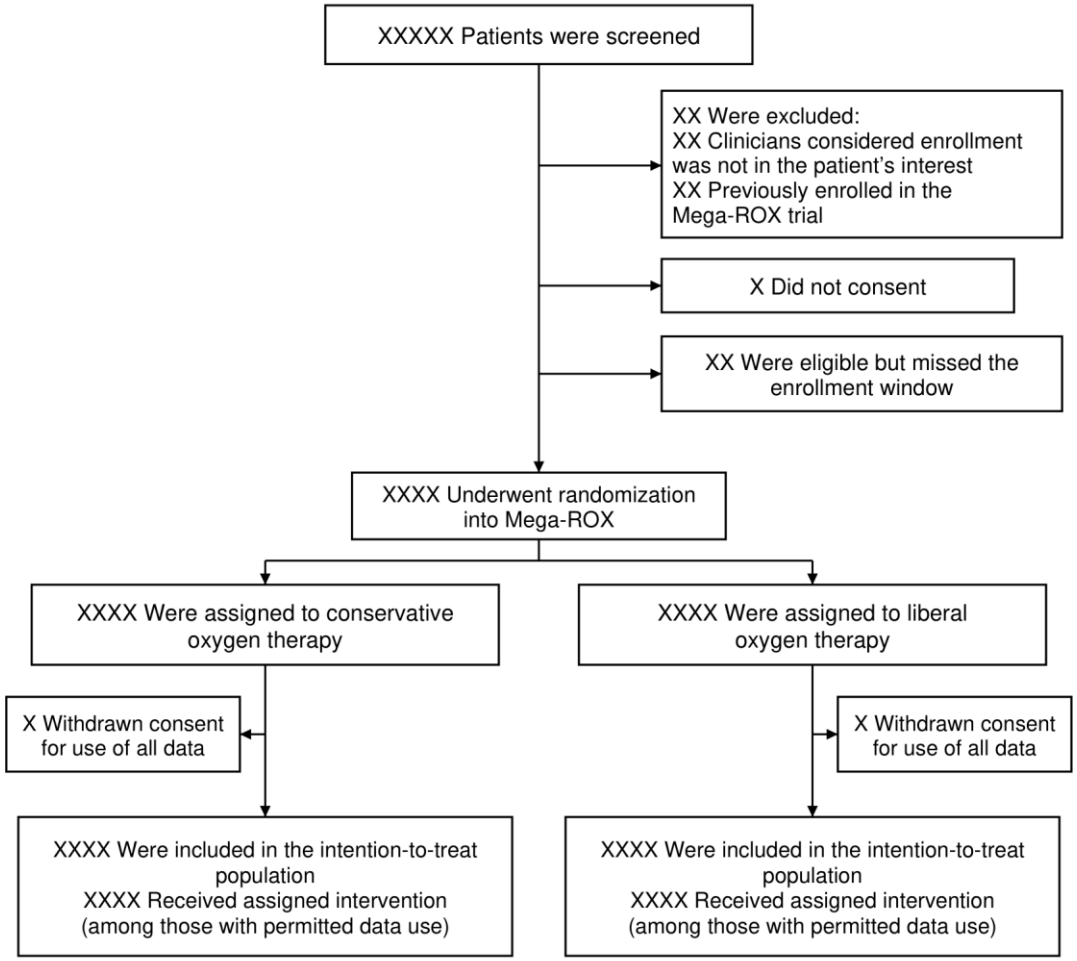


Figure 1. Randomization and Follow-up. The exclusion for enrollment not being in the patient's interests included situations where death was deemed imminent and inevitable. Observed and missing primary outcomes and the reasons for missingness will be reported by allocation. Receipt requires purposeful implementation and is not an intention-to-treat inclusion criterion.

Abbreviations: Mega-ROX, mega randomized registry trial research program.

PANEL A: Kaplan–Meier survival during the index hospitalization

X-axis: days since randomization through day 90, with numbers at risk; Y-axis: probability of survival during the index hospitalization.

The adjusted Cox hazard ratio and 95% CI will be reported.

PANEL B: Forest plot of primary-outcome risk ratios by subgroup

Figure 2. Survival during the Index Hospitalization and Subgroup Analyses of Day-90 Index-Hospital Mortality. Panel A shows Kaplan–Meier survival, ending follow-up at live index-hospital discharge or transfer, day 90, or last reliable in-hospital observation. The formal comparison is log-rank; Cox estimates support it. Panel B shows conservative-to-liberal primary-outcome risk ratios for all patients and the six pre-specified subgroup pairs, using final diagnostic classifications. Squares reflect subgroup size and bars are 95% confidence intervals. Interactions are exploratory.

PANEL A: Live ICU discharge and death before ICU discharge

X-axis: days since randomization through day 90, with numbers at risk; Y-axis: cumulative incidence (%).

The subdistribution hazard ratio and 95% CI will be reported.

PANEL B: Live hospital discharge and death before hospital discharge

X-axis: days since randomization through day 90, with numbers at risk; Y-axis: cumulative incidence (%).

The subdistribution hazard ratio and 95% CI will be reported.

Figure 3. Cumulative Incidence of Live ICU and Hospital Discharge with Death as a Competing Event. Panel A shows first live ICU discharge and death before exit. Panel B shows live index-hospital discharge and death before exit. Fine–Gray models adjust for the three final diagnostic indicators with site-clustered standard errors. Ratios compare conservative with liberal oxygen. A cumulative-incidence median will be reported only if the live-event probability reaches 50%; otherwise it will be reported as not reached. Total ventilation hours cannot supply a liberation-time curve.

Table S1: Study Data Sources for Key Data Points in Each Country/Region*

	Australia	New Zealand	Brazil	Canada	India	Ireland	Italy	Japan	Kuwait	Malaysia	Nepal	Oman	Pakistan	Saudi Arabia SA001	Saudi Arabia SA002
Baseline data															
Age	SD, R	SD, R	SD	SD, R	SD, R	SD	SD	SD	SD	SD, R	SD, R	SD	SD, R	SD	SD
Sex at birth	SD, R	SD, R	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD
ICU admission date	SD, R	SD, R	SD, CRF	SD, R	SD, R	SD, CRF	SD, CRF	SD	SD, CRF	SD, R	SD, R	SD, CRF	SD, R	SD	SD
Hospital admission date	SD, R	SD, R	SD, CRF	SD, R	SD, R	SD, CRF	SD, CRF	SD	SD, CRF	SD, R	SD, R	SD, CRF	SD, R	SD	SD
ICU admission source†	R	R	CRF	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	N/A	CRF
Surgical/medical classification‡	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD
APACHE-II score	R	R	N/A	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	N/A	CRF
SAPS-3	N/A	N/A	CRF	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Outcome data															
In-hospital mortality during index hospitalization within 90 days (primary endpoint)	SD, R	SD, R	SD, CRF	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	SD	CRF
Date of death (if died during index hospitalization within 90 days)	SD, R	SD, R	SD, CRF	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	SD	CRF
Date of ICU discharge (used to calculate ICU length of stay)	SD, R	SD, R	SD, CRF	SD, CRF, R	SD, R	SD, CRF	SD, CRF	SD, R	SD, CRF	SD, R	SD, R	SD, CRF	SD, R	SD	SD, CRF
Date of hospital discharge (used to calculate hospital length of stay)	SD, R	SD, R	SD, CRF	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	SD	CRF
Hospital discharge destination¶	R	R	CRF	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	N/A	CRF
Total hours of invasive ventilation in the index ICU admission	R	R	CRF	CRF, R	R	CRF	CRF	R	CRF	R	R	CRF	R	N/A	CRF
Mortality within 90 days of randomization¥	R	R	N/A	N/A	R	N/A	N/A	N/A	N/A	R	R	N/A	R	N/A	N/A
Date of death within 90 days of randomization¥	R	R	N/A	N/A	R	N/A	N/A	N/A	N/A	R	R	N/A	R	N/A	N/A

* Variables available from more than one source (the study database, a registry or a CRF) will be used to verify that records correspond to the same study participant.
† ICU admission source is categorized as emergency department, operating theater/recovery, ward, another hospital (not ICU), or another ICU.
‡ Study-database ICNARC coding classifies patients as surgical or non-surgical/medical only. It does not distinguish elective from emergency surgery or identify physical ICU admission source; source-of-admission fields are listed separately above.
¶ Hospital discharge destination is categorized as died, home, another medical care facility, or another destination.
¥ Day-90 all-cause mortality includes deaths after hospital discharge. Registry sources are recorded for ANZ, India, Malaysia, Nepal and Pakistan. The pre-specified formal day-90 mortality comparison remains restricted to the ANZ registry analysis population.
Collection notes: CA001 used REDCap for its first 34 participants. SA002 used REDCap, without the Mega-ROX hospital-discharge form. Brazil could record hospital outcomes in both databases. Study-database ICU discharge dates are administrative for India, Malaysia, Nepal and Pakistan. Registry dates will be checked for consistency where available; study-database dates retain precedence for analysis.
Abbreviations: ANZ, Australia/New Zealand; SA001 and SA002, Saudi Arabian study-site identifiers; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRF, case report form, including REDCap; ICU, intensive care unit; N/A, not available; R, registry; SD, study database. Brazil collected SAPS 3 only. Source designations do not establish completeness or successful linkage.

Table S2: Randomization Ratios Applied in the Mega-ROX Trial		
Mega-ROX interim analysis	Hierarchy applied to determining randomization ratios	Ratios applied in each governing diagnostic group: HIE, sepsis, other acute brain condition, or none
N/A	Hypoxic ischemic encephalopathy, then sepsis, and then other brain conditions.	Initial and subsequent allocation probabilities and the hierarchy used for overlapping diagnostic categories
1000 patients	?	?
8000 patients	?	?
16000 patients	?	?
24000 patients	?	?
32000 patients	?	?

Table S3: Pre-specified Oxygen Exposure Metrics

Outcome	**Method of ascertainment***
Physiological outcomes	
The proportion of hours in ICU in CRF days 0–7 after randomization when the SpO_2 was ≥97%.	Daily recorded hours with SpO_2 ≥97% and Total SpO_2 Hours, in CRF days 0–7 after randomization. Daily hours will be summed over days on which both threshold and total hours were recorded and the measure applied. Percentages are 100 × summed threshold hours / summed total hours; hours use the summed numerator.
The total number of hours in ICU in CRF days 0–7 after randomization when the SpO_2 was ≥97%.	Daily recorded hours with SpO_2 ≥97% and Total SpO_2 Hours, in CRF days 0–7 after randomization. Daily hours will be summed over days on which both threshold and total hours were recorded and the measure applied. Percentages are 100 × summed threshold hours / summed total hours; hours use the summed numerator.
The proportion of hours in ICU in CRF days 0–7 after randomization when the SpO_2 was <88%.	Daily recorded hours with SpO_2 <88% and Total SpO_2 Hours, in CRF days 0–7 after randomization. Daily hours will be summed over days on which both threshold and total hours were recorded and the measure applied. Percentages are 100 × summed threshold hours / summed total hours; hours use the summed numerator.
The total number of hours in ICU in CRF days 0–7 after randomization when the SpO_2 was <88%.	Daily recorded hours with SpO_2 <88% and Total SpO_2 Hours, in CRF days 0–7 after randomization. Daily hours will be summed over days on which both threshold and total hours were recorded and the measure applied. Percentages are 100 × summed threshold hours / summed total hours; hours use the summed numerator.
Mean daily PaO_2 in ICU in CRF days 0–7 after randomization	Available scheduled PaO_2 values at 06:00, 12:00, 18:00 and 24:00 in CRF days 0–7; average within participant and day, then give participants equal group weight. Missing scheduled values are not filled.
Highest daily PaO_2 in ICU in CRF days 0–7 after randomization	The separate CRF daily Highest PaO_2 field will be used. The proportion will include participants with at least one recorded value in that field. PaO_2 will be reported in mmHg.
Lowest daily PaO_2 in ICU in CRF days 0–7 after randomization	The separate CRF daily Lowest PaO_2 field will be used. The proportion will include participants with at least one recorded value in that field. PaO_2 will be reported in mmHg.
Process measures	
The proportion of hours in ICU in CRF days 0–7 when the FIO_2 was 0.21	Daily Hours at FIO_2 0.21 and Total FIO_2 hours, collected while ventilated and after extubation in CRF days 0–7. Daily hours will be summed over days on which both room-air and total FIO_2 hours were recorded; percentages are 100 × summed room-air hours / summed total FIO_2 hours.
The total number of hours in ICU in CRF days 0–7 when the FIO_2 was 0.21	Daily Hours at FIO_2 0.21 and Total FIO_2 hours, collected while ventilated and after extubation in CRF days 0–7. Daily hours will be summed over days on which both room-air and total FIO_2 hours were recorded; percentages are 100 × summed room-air hours / summed total FIO_2 hours.
Mean daily FIO_2 (while ventilated) in CRF days 0–7 in ICU	Available scheduled FIO_2 values at 06:00, 12:00, 18:00 and 24:00 in CRF days 0–7 while ventilated; average within participant and day, then give participants equal group weight. Missing scheduled values are not filled.
Highest daily FIO_2 (while ventilated) in CRF days 0–7 in ICU	The separate CRF daily Highest FIO_2 field while ventilated will be used. The number of participants with a recorded value in that field will be reported.
Lowest daily FIO_2 (while ventilated) in CRF days 0–7 in ICU	The separate CRF daily Lowest FIO_2 field while ventilated will be used. The number of participants with a recorded value in that field will be reported.

* Additional collection definitions are provided in the Mega-ROX data dictionary. Each duration summary will use days on which both numerator and denominator were recorded. Each proportion will use its corresponding observed denominator. FIO_2 denotes fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; SpO_2, oxygen saturation measured by pulse oximetry.

Table S4: Body System and Anatomical Site Affected by Illness Resulting in ICU Admission		
Body system and anatomical site involved – n (%)	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)
Respiratory system	xxx (xx.x)	xxx (xx.x)
Upper airway or trachea	xxx (xx.x)	xxx (xx.x)
Bronchi or lower airways	xxx (xx.x)	xxx (xx.x)
Pulmonary vasculature	xxx (xx.x)	xxx (xx.x)
Lungs	xxx (xx.x)	xxx (xx.x)
Pleura or mediastinum	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Coronary arteries	xxx (xx.x)	xxx (xx.x)
Myocardium or cardiac chambers	xxx (xx.x)	xxx (xx.x)
Pericardium, pericardial space or mediastinum	xxx (xx.x)	xxx (xx.x)
Heart valves	xxx (xx.x)	xxx (xx.x)
Conducting system or rhythm disturbances	xxx (xx.x)	xxx (xx.x)
Thoracic aorta	xxx (xx.x)	xxx (xx.x)
Splanchnic or renal vessels	xxx (xx.x)	xxx (xx.x)
Neck or extracranial vessels	xxx (xx.x)	xxx (xx.x)
Limb or limb girdle vessels	xxx (xx.x)	xxx (xx.x)
Great veins	xxx (xx.x)	xxx (xx.x)
Peripheral vasculature, shock or hypertension	xxx (xx.x)	xxx (xx.x)
Pulmonary vasculature	xxx (xx.x)	xxx (xx.x)
Uterine or ovarian vessels	xxx (xx.x)	xxx (xx.x)
Abdominal aorta	xxx (xx.x)	xxx (xx.x)
Iliac vessels	xxx (xx.x)	xxx (xx.x)
Gastrointestinal system		
Mouth or pharynx	xxx (xx.x)	xxx (xx.x)
Esophagus	xxx (xx.x)	xxx (xx.x)
Stomach	xxx (xx.x)	xxx (xx.x)
Duodenum	xxx (xx.x)	xxx (xx.x)
Small bowel	xxx (xx.x)	xxx (xx.x)
Large bowel, rectum or anus	xxx (xx.x)	xxx (xx.x)
Liver or biliary tree	xxx (xx.x)	xxx (xx.x)
Spleen	xxx (xx.x)	xxx (xx.x)
Pancreas	xxx (xx.x)	xxx (xx.x)
Abdominal wall or peritoneum	xxx (xx.x)	xxx (xx.x)
Neurological system		
Head (extracranial), neck or eyes	xxx (xx.x)	xxx (xx.x)
Brain, CSF, meninges or skull vault	xxx (xx.x)	xxx (xx.x)
Spinal cord	xxx (xx.x)	xxx (xx.x)
Peripheral nervous system	xxx (xx.x)	xxx (xx.x)
Neuro-muscular junction	xxx (xx.x)	xxx (xx.x)

Table S4 continued: Body System and Anatomical Site Affected by Illness Resulting in ICU Admission		
Body system and anatomical site involved – n (%)	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)
Genito-urinary system		
Kidney or ureter	xxx (xx.x)	xxx (xx.x)
Bladder or urethra	xxx (xx.x)	xxx (xx.x)
Ovary, fallopian tubes, uterus or genitalia (non-obstetric)	xxx (xx.x)	xxx (xx.x)
Ovary, fallopian tubes, uterus or genitalia (obstetric)	xxx (xx.x)	xxx (xx.x)
Testes, prostate or penis	xxx (xx.x)	xxx (xx.x)
Endocrine, metabolic, thermoregulatory, and poisoning		
Thyroid	xxx (xx.x)	xxx (xx.x)
Adrenal	xxx (xx.x)	xxx (xx.x)
Endocrine pancreas	xxx (xx.x)	xxx (xx.x)
Parathyroids	xxx (xx.x)	xxx (xx.x)
Ovaries	xxx (xx.x)	xxx (xx.x)
Thermoregulation	xxx (xx.x)	xxx (xx.x)
Body fluids or tissues	xxx (xx.x)	xxx (xx.x)
Body composition	xxx (xx.x)	xxx (xx.x)
Chromosomal abnormalities	xxx (xx.x)	xxx (xx.x)
Poisoning	xxx (xx.x)	xxx (xx.x)
Hematological / immunological		
Blood	xxx (xx.x)	xxx (xx.x)
Bone marrow	xxx (xx.x)	xxx (xx.x)
Musculoskeletal and skin		
Vertebral column	xxx (xx.x)	xxx (xx.x)
Pelvis, long bones, or joints	xxx (xx.x)	xxx (xx.x)
Muscles or connective tissue	xxx (xx.x)	xxx (xx.x)
Skin	xxx (xx.x)	xxx (xx.x)
Psychiatric	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)

Table S5: Comorbid Conditions		
	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)
Comorbid conditions – n (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Hepatic	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Immunosuppression by disease	xxx (xx.x)	xxx (xx.x)
Immunosuppression by therapy	xxx (xx.x)	xxx (xx.x)

Table S6: Additional Details on Diagnostic Categories, Surgical Admissions and Key Pathological Processes

	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)
Overlap of subgroups– n (%)		
Confirmed or suspected hypoxic ischemic encephalopathy alone	xxxx (xx.x)	xxxx (xx.x)
Confirmed or strongly suspected sepsis alone	xxxx (xx.x)	xxxx (xx.x)
Acute brain pathology other than hypoxic ischemic encephalopathy only	xxxx (xx.x)	xxxx (xx.x)
Confirmed or suspected hypoxic ischemic encephalopathy AND confirmed or strongly suspected sepsis	xxxx (xx.x)	xxxx (xx.x)
Confirmed or suspected hypoxic ischemic encephalopathy AND acute brain pathology other than hypoxic ischemic encephalopathy	xxxx (xx.x)	xxxx (xx.x)
Acute brain pathology other than hypoxic ischemic encephalopathy AND confirmed or strongly suspected sepsis	xxxx (xx.x)	xxxx (xx.x)
Confirmed or suspected hypoxic ischemic encephalopathy AND confirmed or strongly suspected sepsis AND acute brain pathology other than hypoxic ischemic encephalopathy	xxxx (xx.x)	xxxx (xx.x)
Misclassified stratification variables – n/N (%)†		
At least one of the three diagnostic variables	xxx/xxx (xx.x)	xxx/xxx (xx.x)
HIE	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Non-HIE brain condition	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Sepsis	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Surgical/medical classification – n (%)		
Surgical	xxxx (xx.x)	xxxx (xx.x)
Non-surgical/medical	xxxx (xx.x)	xxxx (xx.x)
Pathological processes– n (%)		
Coma / encephalopathy	xxx (xx.x)	xxx (xx.x)
Infection	xxx (xx.x)	xxx (xx.x)
Inflammation	xxx (xx.x)	xxx (xx.x)
Hemorrhage	xxx (xx.x)	xxx (xx.x)
Hematological	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Tumor or malignancy	xxx (xx.x)	xxx (xx.x)

* The top 10 process categories will be listed; examples are shown. Surgical/medical classification uses study-database ICNARC coding. Final diagnostic categories are used for the overlap summaries.
† Misclassification is a difference between the originally selected and final presence/absence values. Denominator N requires both values for that variable, or all three paired values for the overall summary; unavailable pairs will be counted separately. Categories can overlap; each participant contributes once to the overall total. HIE denotes hypoxic ischemic encephalopathy; non-HIE, other acute brain injury or condition.

Table S7: Representativeness of the Trial Participants*		
ANZ admissions with unplanned invasive ventilation	Enrolled	Other registry patients meeting the shared criteria
Patients, no.	xxxxx	xxxxx

* ANZ trial participants and other registry admissions will be compared at the same participating ICUs and during the same recruitment periods, using criteria observable in both data sources, as specified in Section 5.

Table S8: Protocol Deviations and Delivery of Allocated Treatment*

Nature of deviation	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Allocated treatment never given – no. (%)	xxx (xx.x)	xxx (xx.x)
Inadvertently received opposite treatment	xxx (xx.x)	xxx (xx.x)
Ineligible: Admitted into ICU for palliative care	xxx (xx.x)	xxx (xx.x)
Allocated strategy withheld throughout the ICU admission because the treating clinician determined it was not in the patient's best interests (never received)	xxx (xx.x)	xxx (xx.x)
Allocation not communicated to bedside; neither study strategy purposefully implemented	xxx (xx.x)	xxx (xx.x)
Allocated strategy never purposefully implemented; reason unclear	xxx (xx.x)	xxx (xx.x)
Extubation or death before the allocated strategy could be purposefully implemented	xxx (xx.x)	xxx (xx.x)
Transfer from a study ICU to a non-study ICU before the allocated strategy could be purposefully implemented	xxx (xx.x)	xxx (xx.x)
Received allocated treatment but one or more deviations were recorded		
FIO_2 greater than 0.21 and not reduced when the SpO_2 was 95% or more	xxx (xx.x)	Not applicable
Used an FIO_2 less than 0.3 during mechanical ventilation	Not applicable	xxx (xx.x)

*Receipt requires purposeful implementation at some point; initially withheld treatment later implemented counts as received. Eligibility and receipt are separate. Deviation categories can overlap.
Abbreviations: FIO_2: fraction of inspired oxygen; ICU: intensive care unit; PaO_2: arterial partial pressure of oxygen. SaO_2: arterial oxygen saturation. SpO_2: arterial oxygen saturation measured by peripheral pulse oximetry;

Table S9: Additional Analyses of Primary and Secondary Outcomes*

	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)	Difference or geometric mean ratio† (95% CI)	Relative risk‡ (95% CI)
Primary outcome				
Mortality during the index hospitalization within 90 days, n (%)				
Primary analysis	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis: age and sex, and further clinically meaningful baseline imbalances			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis: eligible participants only			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis: eligible participants who received allocation			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis: originally selected HIE, non-HIE and sepsis strata			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis: inverse-probability weighted primary model with epoch			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Multiple imputation if extreme scenarios change the primary inference; observed-outcome results will also be reported			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis: worst–best and best–worst missing primary outcomes			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Non-medically-indicated discharge: conservative death / liberal non-event			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Non-medically-indicated discharge: conservative non-event / liberal death			x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Secondary outcomes				
Geometric mean total hours of invasive ventilation in ICU, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean total hours of invasive ventilation in ICU for survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)		
Geometric mean total hours of invasive ventilation in ICU, for non-survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)		
Completed ICU duration: median (IQR), days	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Adjusted median difference x.xx (x.xx to x.xx)	
Geometric mean ICU length of stay, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean ICU length of stay for survivors, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)		
Geometric mean ICU length of stay for non-survivors, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)		
Completed hospital duration: median (IQR), days	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Adjusted median difference x.xx (x.xx to x.xx)	
Geometric mean hospital length of stay, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean hospital length of stay for survivors, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)		
Geometric mean hospital length of stay, for non-survivors, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)		

* Ordinary confidence intervals for supporting and secondary analyses are not multiplicity-adjusted. Positive-only geometric means have their observed denominator and zero counts reported. Completed, right-censored and missing completed-duration counts will be reported by allocation.

† Primary-outcome and home-discharge risk differences use binomial identity-link models with the primary adjustment set, using originally selected diagnostic indicators for the stratification-misclassification sensitivity analysis. Ratios of geometric means for total ventilation hours and observed completed ICU/hospital durations compare conservative with liberal oxygen, using diagnosis-adjusted log-linear regressions with site-clustered standard errors. ICU/hospital duration summaries are distinct from censored time to live discharge. Supporting conditional median differences in completed ICU and hospital duration are conservative minus liberal, estimated by quantile regression with the same diagnostic adjustment and site-clustered standard errors. These completed-duration analyses use all available index-episode follow-up, including beyond day 90; right-censored elapsed stays are excluded.
‡ Risk ratios use log-binomial models adjusted for final HIE, sepsis and other brain conditions, with a random site intercept; the stratification-misclassification sensitivity analysis substitutes the originally selected diagnostic indicators. The model-convergence sequence in Section 6 applies to both risk-ratio and risk-difference models if required. Additional adjustment includes age and sex and, in a further model, clinically meaningful baseline imbalances. APACHE II and SAPS 3 are not adjustment covariates. Survival strata use the end status of the relevant episode; ventilation strata use ICU-episode survival.

Supplementary figures

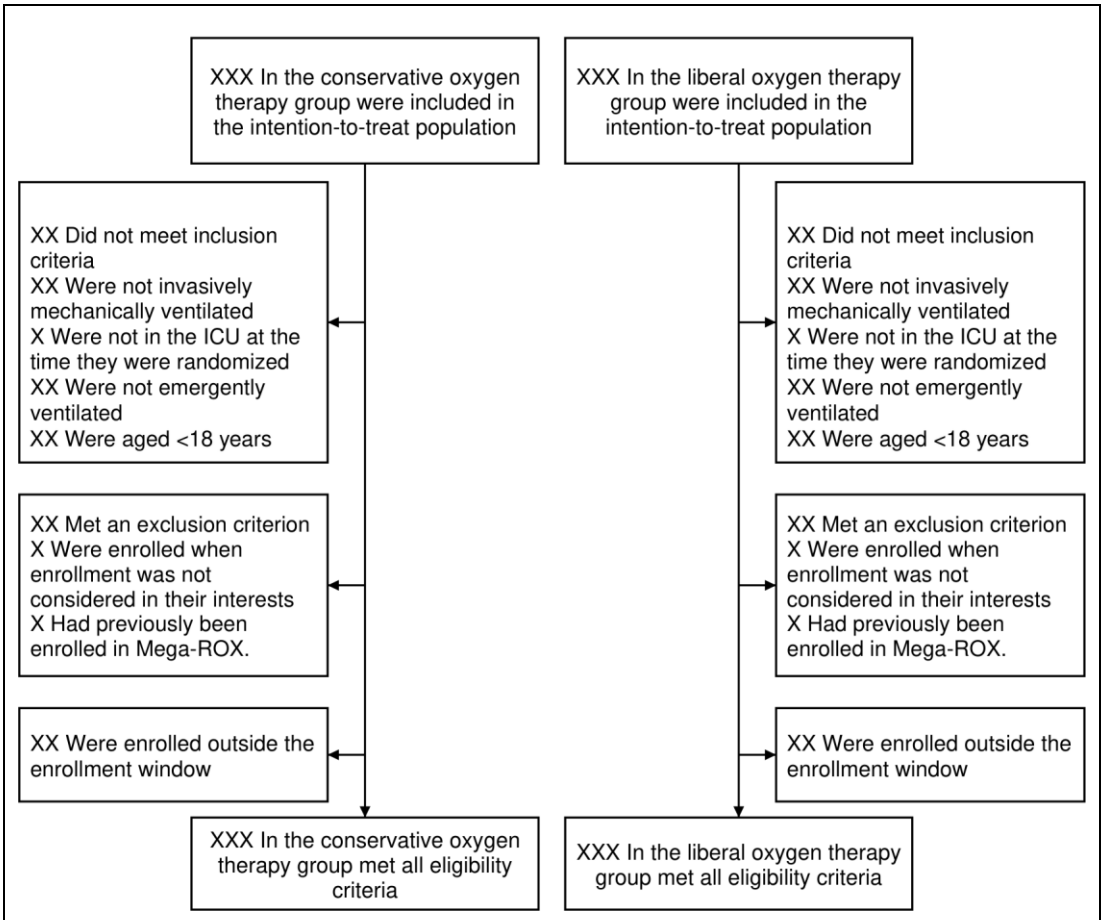


Figure S1. Protocol Deviations Affecting Trial Eligibility. The overarching ventilation, ICU, exclusion and enrollment-window criteria will be applied. Categories may overlap. Eligibility and purposeful strategy receipt are assessed separately.

Abbreviations: Mega-ROX, mega randomized registry trial research program.

PANEL A: Mean FiO_2 by treatment group

(X-axis: days 0 to 7 with number of observations per day; Y-axis: FiO_2)

PANEL B: Highest FiO_2 by treatment group

(X-axis: days 0 to 7 with number of observations per day; Y-axis: FiO_2)

PANEL C: Lowest FiO_2 by treatment group

(X-axis: days 0 to 7 with number of observations per day; Y-axis: FiO_2)

Figure S2. Fraction of Inspired Oxygen by Treatment Group. Panel A uses each participant's mean of available scheduled 06:00, 12:00, 18:00 and 24:00 FiO_2 readings in CRF days 0–7. Panels B and C use the separate daily Highest and Lowest fields. Equally weighted group means, standard errors and the number of contributing participants for each plotted measure will be shown. These fields apply while ventilated. The room-air duration block also includes time after extubation.

PANEL A: Mean PaO_2 by treatment group

(X-axis: days 0 to 7 with number of observations per day; Y-axis: PaO_2)

PANEL B: Highest PaO_2 by treatment group

(X-axis: days 0 to 7 with number of observations per day; Y-axis: PaO_2)

PANEL C: Lowest PaO_2 by treatment group

(X-axis: days 0 to 7 with number of observations per day; Y-axis: PaO_2)

Figure S3. Arterial Partial Pressure of Oxygen by Treatment Group. Panel A uses each participant's mean of available scheduled 06:00, 12:00, 18:00 and 24:00 PaO_2 readings in CRF days 0–7. Panels B and C use the separate daily Highest and Lowest fields. Equally weighted group means, standard errors and the number of contributing participants for each plotted measure will be shown. PaO_2 will be reported in mmHg.