Mega ROX Sepsis
Detailed Statistical Analysis Plan

Version 2.0 | 9 November 2026

Finalized blinded to study data prior to database lock.

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This plan specifies the population, outcomes and analyses for the nested trial. It follows the structure of the final LOGICAL SAP and applies the statistical methods in the overarching Mega-ROX SAP, version 2.0 dated 9 November 2026. Trial-specific definitions and amendments are set out below. The appendices contain the planned publication tables and figures.

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Section 1 Administrative Information

1. Title

Mega randomized registry trial comparing conservative versus liberal oxygenation targets in adults with sepsis in the intensive care unit Mega ROX Sepsis

This detailed plan specifies the comparison of liberal with conservative oxygen therapy in the pre-specified sepsis population within Mega-ROX. It retains the published sepsis hypothesis and applies the general methods in the current overarching SAP to the outcomes and data available for this population.

2. Trial registration

The Mega-ROX research program was prospectively registered with the Australian and New Zealand Clinical Trials Registry ACTRN12620000391976. Mega-ROX Sepsis is a pre-specified nested trial within that registration. The registration identifies the parent research program; the Sepsis-specific hypothesis, population and analyses are specified in the Sepsis protocol and this detailed SAP.

3. SAP version

Version 2.0 dated 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/. Database-lock and results-access dates will be documented in the final report.

4. Protocol version

This document follows the published Mega-ROX Sepsis protocol and SAP: Young PJ et al. Critical Care and Resuscitation. 2023;25:106–112. doi:10.1016/j.ccrj.2023.04.008 [1]. General statistical methods follow the overarching detailed Mega-ROX SAP version 2.0 dated 9 November 2026 [2]. The overarching published protocol [3] describes the design and allocation system. Material amendments will be dated and their timing relative to access to results disclosed.

This document specifies the analysis plan for the Sepsis population, liberal-versus-conservative contrast, diagnostic sensitivity analyses, the subgroup analyses and planned outputs. Necessary differences from the published Sepsis plan are recorded in section 34.

5. SAP revisions

This SAP provides the additional operational definitions, analysis populations, modeling details and planned outputs needed to implement the published Mega-ROX Sepsis analysis plan. The principal revisions reflect the latest overarching SAP and the limits of the fields actually collected.

Material revisions will be dated and described, including their rationale and timing relative to access to treatment and outcome results. Version 2.0 was finalized on 9 November 2026, blinded to study data and prior to database lock. The online posting date is 10 November 2026. Database-lock and first treatment-results-access dates will be documented.

6. Names and affiliations

Prepared for approval by Professor Jessica Kasza, Monash University, and Professor Paul Young, Intensive Care Unit, Wellington Hospital, and Medical Research Institute of New Zealand.

Signature of senior statistician Jessica Kasza:  _____ Date: 9 November 2026

Signature of chief investigator Paul Young:  _____ Date: 9 November 2026

Section 2 Introduction

7. Brief background and rationale

The published protocol provides the detailed rationale [1]. Oxygen is routinely administered during invasive ventilation in sepsis. Liberal oxygen may provide a margin against hypoxemia and support oxygen-dependent antimicrobial and tissue-repair mechanisms; excessive oxygen exposure may also cause harm. Existing evidence did not establish which regimen used in Mega-ROX should be preferred.

The nested comparison will be reported independently of whether the overarching sepsis-by-treatment interaction is significant. Evidence that effects differ between patients with and without sepsis requires that interaction analysis in the overarching trial.

8. Objectives

Research hypothesis: Among adults with confirmed or strongly suspected sepsis before randomization who receive unplanned invasive mechanical ventilation in ICU, liberal oxygen therapy, compared with conservative oxygen therapy, reduces in-hospital all-cause mortality up to 90 days after randomization.

The primary objective is to estimate the effect on death during the index hospital admission within 90 days. Secondary objectives concern survival during the index hospitalization, live ICU and hospital discharge, total ventilation hours, direct discharge home and registry-ascertained 90-day all-cause mortality.

Oxygen exposure, delivery of the allocated strategy and reported adverse events will be described.

Section 3 Trial Methods

9. Trial design

Investigator-initiated, international, multicenter, individually randomized, parallel-group, two-sided superiority trial nested within Mega-ROX. Its population may overlap with Mega-ROX HIE and Brains when more than one condition was present before randomization.

Allocation was open to bedside clinicians. The diagnosis governing the adaptive allocation probability need not have been sepsis. Other treatment was provided at the clinician's discretion within the protocol.

10. Randomization

A secure centralized web interface used a computer-generated sequence and concealed upcoming allocation. No stratification or permuted blocks were used. Permitted liberal-to-conservative ratios were 1.05:1, 1:1 and 1:1.05. The initial sepsis ratio favored liberal oxygen, reflecting the ICU-ROX sepsis estimate [1,3].

The algorithm used interim estimates for HIE, sepsis, non-HIE brain conditions and patients with none of these conditions. For overlapping diagnoses, the hierarchy in the overarching protocol determined the applied probability. Subsequent ratios were not disclosed to investigators or the management committee.

The primary model adjusts for the other final diagnostic categories. A supporting analysis uses inverse probabilities of the assigned treatment and categorical randomization epoch. Sepsis membership is not restricted to participants whose sepsis diagnosis governed randomization, and it also includes participants whose sepsis was confirmed before randomization but whose website sepsis response was inadvertently recorded as 'no'.

11. Sample size

The sepsis sample size depended on its proportion within the overarching target of 40,000 participants. The preceding detailed sepsis SAP records an initial registration target of 10,362 participants based on ICU-ROX. With a conservative-group mortality risk of 25.6%, that sample provided more than 90% power to detect an absolute difference of 2.8 percentage points at a two-sided alpha of 0.05.

The projection was revised to approximately 13,000 based on the sepsis proportion at the fourth interim analysis. With a conservative-group risk of 25%, 13,000 gives 90% power for an absolute difference of 2.42 percentage points [1]. These are planning assumptions. Achieved enrollment and estimate precision will be reported without post hoc power.

12. Framework

The primary comparison uses a superiority framework with two-sided testing. Liberal oxygen is the intervention and conservative oxygen the comparator. Risk ratios and geometric-mean ratios compare liberal with conservative oxygen; risk differences and median differences are liberal minus conservative. Risk differences will be expressed in percentage points. 95% confidence intervals will be reported. The pre-specified sepsis comparison does not depend on a significant overarching interaction.

For mortality, a risk ratio below 1 or a negative risk difference favors liberal oxygen. For live discharge, a subdistribution hazard ratio above 1 indicates a greater cumulative incidence of live discharge in the liberal group. Reporting will follow CONSORT 2025 as specified in the overarching SAP [2].

13. Statistical interim analyses and stopping guidance

Overarching reviews occurred after 1,000, 8,000, 16,000, 24,000 and 32,000 enrollments. The initial review primarily assessed recruitment and could update allocation probabilities. Subsequent efficacy reviews used a symmetric Haybittle–Peto boundary of $P<0.001$, preserving final alpha 0.05 [2,3].

The published sepsis plan specified a sepsis-specific efficacy review only with treatment-response heterogeneity at $P<0.05$ and the same $P<0.001$ stopping boundary [1]. The report will distinguish

scheduled overarching reviews from nested reviews actually undertaken. Actual recommendations and adaptations will be reported from approved records.

14. Timing of final analysis

Final analysis will follow completion of relevant 90-day follow-up and SAP approval. Analysis development will use dummy labels where feasible, and two statisticians will independently check primary results as envisaged in the published plan. The dates of SAP finalization, public posting, database lock and access to treatment results will be reported.

15. Timing of outcome assessments

The primary interval is randomization through day 90. Survival and live-discharge analyses use randomization as time zero and endpoint-specific earlier ends of follow-up. Recorded total ventilation hours describe the completed index ICU episode and may include pre-randomization ventilation. Supporting completed ICU and hospital episode durations will use all available follow-up to the recorded episode end or death, including beyond day 90. All-cause day-90 mortality requires post-discharge ascertainment in the predefined ANZ registry population.

Oxygen CRF columns are labeled day 0 through day 7; they do not imply eight full days or 168 observed hours. Collection follows measure-specific CRF rules and ends at the recorded end of collection, death or first ICU discharge, whichever occurs first.

Section 4 Statistical Principles

16. Level of statistical significance

The primary risk-ratio treatment test is two-sided at 5%. One primary P value will be used consistently across manuscript and tables. Unless otherwise stated, tests are two-sided. Multiplicity corrections for secondary outcomes are described in section 17; sensitivity, subgroup and exposure comparisons remain supporting or exploratory.

17. Adjustment for multiplicity

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 27. 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. 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 (binary risk-ratio treatment test). The binary risk-ratio treatment test for ANZ all-cause day-90 mortality is the sixth comparison when included.

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, $m - 1$, …, 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 in Table S16. 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 and its result 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 log-rank test. Supporting Cox, duration, geometric-mean, sensitivity, subgroup and exposure analyses will not add to or replace the formal tests.

18. Confidence intervals

All confidence intervals will be two-sided 95% intervals. Secondary, sensitivity, subgroup and exposure intervals will be ordinary pointwise intervals without multiplicity adjustment. Confirmatory conclusions for secondary outcomes will use their Holm-Bonferroni-adjusted P values. Each effect estimate will be reported with its units and direction.

19. Adherence and protocol deviations

Conservative oxygen used the lowest F_IO_2 achieving the default SpO_2 lower limit of 91%, reducing to room air when possible. SpO_2 above 94% was to be avoided, with an upper alarm of 95% during supplemental oxygen. Liberal oxygen was delivered as directed by the clinician with minimum F_IO_2 0.30 during invasive ventilation. Assigned treatment applied in ICU until discharge or day 90, and resumed on ICU readmission during the index admission. Protocol-permitted transport and procedural changes were not deviations.

Participants will remain in their allocated groups despite protocol deviations. The number of affected participants, episodes and reasons will be reported where collected; participant and episode counts will be distinguished. 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.

Oxygen exposure measurement and comparisons are specified in section 27 and Table S3.

20. Analysis populations and estimand

The primary population comprises unique randomized participants with confirmed or strongly suspected sepsis before randomization according to the final baseline sepsis category (i.e. have a final recorded classification of sepsis), and permission to use data. Final classification agrees with the overarching SAP. Non-receipt, ineligibility, cessation and crossover do not remove participants. Only the first allocation is used after duplicate randomization. Treatment withdrawal alone does not withdraw permission to use data.

The estimand, fully described in the table below, is the liberal-to-conservative relative risk of in-hospital death within 90 days, with liberal-minus-conservative absolute difference in percentage points. Non-receipt and deviations are accounted for via a treatment-policy strategy. Live discharge from the index hospital before day 90, including non-medically-indicated discharge, or verified survival in hospital at day 90 is a non-event. Deaths after discharge are counted as in-hospital survival.

The primary analysis will use observed outcomes, with missing-data sensitivity analyses performed as specified in section 31. Adjustment will include final HIE and non-HIE brain-condition indicators; sepsis is constant within this population. Supporting populations will comprise eligible participants only and eligible participants who purposefully received their assigned strategy. The diagnostic sensitivities will consider concordant original-and-final sepsis-Yes, original sepsis-Yes and expanded populations as specified in section 29. Participants with an original sepsis-Yes response and final sepsis-No classification will be outside the principal final-category population and included in the relevant diagnostic sensitivities. Counts in each original-versus-final classification will be reported by allocation.

Objective: To determine whether liberal oxygen therapy, compared to conservative oxygen therapy, decreases the risk of in-hospital all-cause mortality up to 90 days from the date of randomization for patients with sepsis.

Estimand: Relative risk of incidence of in-hospital all-cause mortality up to 90 days from the date of randomization among adult ICU patients with sepsis who receive unplanned invasive mechanical ventilation, assigned to liberal oxygen therapy, relative to conservative oxygen therapy.

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.

ESTIMAND	**ANALYSIS**
Target population: adult patients with sepsis in the ICU who receive unplanned invasive mechanical ventilation.	**Analysis set**: All randomized participants who had confirmed or strongly suspected sepsis at randomization, except those for whom consent for the use of study data is withdrawn. Patients assigned to receive liberal oxygen therapy through randomization will be the treatment group, patients assigned to receive conservative 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 using 20 datasets will be performed if either extreme scenario changes the conclusion of the primary comparison at the two-sided 5% significance level. Suitable overarching-trial imputations will be reused if available; otherwise, imputations will be generated only within the final sepsis-Yes cohort and the relevant outcome-specific collection population (section 31). **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 participants who purposefully received their assigned strategy. In addition to excluding ineligible participants, eligible participants who never purposefully received their assigned strategy will be excluded from this analysis. Receipt will be determined as specified in section 19. 3) Diagnostic sensitivity 1: participants with both an original sepsis-Yes response at randomization and a final sepsis-Yes classification, and permission to use data.

	4) Diagnostic sensitivity 2: patients who were initially identified as having sepsis and permission to use data only. 5) Diagnostic sensitivity 3: patients who were ultimately identified as having sepsis plus those initially identified as having sepsis with diagnosis later revised to no sepsis, plus permission to use data. 6) 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: Risk ratio of in-hospital all-cause mortality up to 90 days from the date of randomization comparing liberal with conservative oxygen therapy, and risk differences expressed as liberal minus conservative.	**Analysis approach**: The risk ratio 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 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. Convergence sequence as in Section 27 applies.

Section 5 Trial Population

21. Screening data

The CONSORT diagram will show screening where collected, eligibility, exclusions by reason, eligible patients missed within the window, randomization, data-use exclusions and final sepsis population. Missing screening records are not evidence that no participants were screened or missed.

Cross-classification of original randomization and final baseline sepsis status will be described by allocated group, including all recorded Yes/No combinations. These counts describe cohort membership and the diagnostic sensitivity analyses. They do not change the allocation probabilities actually applied.

22. Eligibility

Patients were aged ≥18 years, had confirmed or strongly suspected sepsis before randomization and received unplanned invasive mechanical ventilation in ICU. Unplanned ICU admission is not a separate eligibility requirement. Sepsis was life-threatening organ dysfunction due to a dysregulated host response to infection [1,5]. Enrollment was required within 12 hours of eligibility.

Previous enrollment and enrollment not in the patient's best interests were exclusions, including clinically indicated or contraindicated regimens or death deemed imminent and inevitable. Patients not enrolled within 12 hours were eligible but missed.

23. Recruitment

Recruitment dates, participating ICUs and countries, allocated numbers and the derivation of the sepsis cohort from the overarching population will be reported. Participant flow will distinguish data-use exclusions, missing outcomes, original-versus-final diagnostic classification and sensitivity-analysis exclusions.

24. Withdrawal and follow-up

Non-provision or withdrawal of permission to use data will be reported separately from treatment or follow-up withdrawal. Data will be retained and analyzed according to the applicable consent provisions. Numbers and recorded reasons for missing outcomes will be reported by allocation, distinguishing structural non-collection and unresolved linkage where relevant. Reasons will not be inferred from absent values.

Live hospital discharge establishes a non-event for in-hospital mortality but does not establish survival through day 90. A verified binary death will remain usable when its exact time is unavailable; the denominator with exact timing will be reported separately. For the formal mortality, survival and live-discharge endpoints, follow-up will end at the relevant event, day 90 or the last reliable observation, as defined for each endpoint. Supporting completed ICU and hospital durations will use the available episode follow-up described in section 27.

25. Baseline descriptive measures

Continuous variables will be summarized as means and standard deviations or medians and interquartile ranges, as appropriate to their distributions. Categorical variables will be summarized as counts and percentages with observed denominators and missing counts. No allocation-group baseline significance tests will be performed. Table 1 will contain age, sex, body-mass index, preadmission frailty, admission source, admission-to-randomization intervals, APACHE II and SAPS 3 where collected, sepsis source, COVID-19 and baseline oxygenation. Tables S4–S8 will present the detailed diagnoses.

Baseline PaO_2 will be the last arterial blood gas before randomization, and PaO_2/FIO_2 will use the FIO_2 recorded with that sample. An unrelated oxygen measurement or FIO_2 alone will not supply the ratio.

Surgical admission is identified through ICNARC coding at all sites. ANZ representativeness will be described by comparing trial participants with registry admissions at participating ICUs during the same recruitment periods, using common recorded sepsis, unplanned invasive-ventilation and baseline features (Table S9).

Where the primary outcome is missing, baseline characteristics will also be summarized by primary-outcome availability, following the overarching SAP. Those comparisons, together with clinical knowledge and the analysis covariates, can inform auxiliary variables if outcome imputation is required. They are distinct from tests of baseline balance between treatment groups.

Section 6 Analysis

26. 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.	Final-baseline sepsis cohort with observed outcome	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.	Final-baseline sepsis cohort with usable timing	Log-rank test. Supporting Cox hazard ratios are reported separately.
Live ICU discharge	First live exit from index ICU; death before exit is a competing risk. Follow to day 90.	Final-baseline sepsis cohort with usable timing	Treatment-effect test from a Fine–Gray model adjusted for 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.	Final-baseline sepsis cohort with usable timing	Treatment-effect test from a Fine–Gray model adjusted for 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.	Sepsis ventilation 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.	Sepsis destination collection population excluding SA001	Random-site-intercept binary risk-ratio model.
All-cause day-90 mortality	Death by day 90, including after hospital discharge; reliable survival through day 90 establishes survival.	Sepsis participants in the predefined ANZ registry coverage population	Random-site-intercept binary risk-ratio model.

Data sources. The study database will be used for variables recorded in both the study database and a registry. Variables recorded only in a registry or only in the CRF will be taken from that source. Table S1 describes source availability; source designations do not establish completeness or successful linkage. Outcome-specific collection populations and observed analysis denominators will be reported separately.

27. Analysis methods

Primary binary outcome and secondary binary outcomes. A log-binomial model with treatment allocation, final HIE and final non-HIE brain-condition indicators and a random intercept for site will estimate the adjusted liberal-to-conservative risk ratio. Liberal oxygen will be the treatment group and conservative oxygen the reference. A separate binomial model with identity link and the same

covariates and random site intercept will estimate the risk difference. The risk-ratio treatment test will supply the primary P value. Events, observed denominators, proportions, risk ratios, risk differences and 95% confidence intervals will be reported.

Convergence. The overarching sequence will be applied separately to each link. If the initial model fails to converge, the first convergent model in the following sequence will be used: the same model with site-clustered robust standard errors instead of a random site intercept; the original random-intercept model after pooling sites with fewer than 10 participants; that model after pooling sites with fewer than 20 participants; and random-intercept models omitting HIE, omitting non-HIE brain conditions, then omitting both. The actual link, covariates and site handling will be reported. If the sequence yields no estimate, the result will be reported as unavailable.

Survival. Kaplan–Meier curves will display survival during the index hospitalization, and allocations will be compared using a two-sided log-rank test, the formal survival test within the Holm-Bonferroni family. Treatment-only and treatment-plus-HIE/non-HIE Cox models with site-clustered robust standard errors will provide supporting hazard ratios and 95% confidence intervals. Follow-up will end at index-hospital death, live discharge or transfer, day 90 or the last reliable observation. Postdischarge deaths will not enter the all-site analysis. The separate ANZ all-cause survival display is subject to the linkage requirement below.

The overarching small-site pooling sequence will apply to survival models if needed, pooling sites with fewer than 10 participants, then fewer than 20, and refitting the model. Proportional hazards will be assessed using Schoenfeld residuals; departures will be reported without replacing the planned models or log-rank test. Event times will use the recorded dates and times. When a discharge date is known but its time is unavailable, midday will be assumed as specified in the overarching SAP, and the number affected will be reported. Known binary outcomes will remain in their analyses when exact times are unavailable.

Live ICU and hospital discharge. Separate Fine–Gray models with treatment allocation, final HIE and final non-HIE brain-condition indicators and site-clustered robust standard errors will be fitted, with death before the relevant exit as the competing event. The same small-site pooling sequence will apply if required. Subdistribution hazard ratios, 95% confidence intervals and each formal treatment P value will be reported. A ratio above 1 will indicate greater cumulative incidence of live discharge in the liberal group. Live-discharge and competing-death cumulative incidence functions will be displayed. A median time will be reported only if the corresponding live-discharge cumulative incidence reaches 50%; otherwise it will be reported as not reached. Any median among observed live discharges will be identified separately as descriptive.

Ventilation. Median quantile regression for completed total invasive ventilation hours will include treatment allocation, final HIE and final non-HIE brain-condition indicators and site-clustered robust standard errors using qreg2 in Stata or an equivalent implementation. The treatment coefficient will estimate the conditional median difference in hours, liberal minus conservative, and its test will supply the formal ventilation P value. This estimate may differ from the observed marginal-median difference. Zero recorded hours will be retained and counted separately.

Supporting durations. Corresponding quantile models will compare completed ICU and hospital episode lengths from randomization to the recorded episode end or death, using all available follow-up, including beyond day 90. Patients still in the ICU or hospital at the last available follow-up will be right-censored at that time. Censored elapsed times will not be treated as completed durations in the quantile or log-linear models; their numbers and available follow-up will be reported by allocation. Log-linear regressions of positive completed ventilation, ICU and hospital durations will include treatment allocation, final HIE and final non-HIE brain-condition indicators and site-clustered robust standard errors. Exponentiated treatment coefficients will estimate liberal-to-conservative ratios of geometric means. Observed medians and quartiles, geometric means and 95% confidence intervals, and summaries stratified by survival to the relevant episode end will be reported; ventilation summaries will use ICU-episode survival. Survivor-restricted summaries will be descriptive because they condition on a post-randomization event.

Home discharge and ANZ mortality. The primary log-link and separate identity-link models and their convergence sequences will be applied within the respective collection populations. Eligible and observed denominators and events will be reported. ANZ mortality will include post-discharge deaths, with registry eligibility, coverage and linkage completeness described. Structurally uncollected outcomes will not be imputed. The risk-ratio treatment tests will be the formal secondary comparisons. 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.

Table 3 and supplementary outputs will label risk ratio, risk difference, hazard ratio, subdistribution hazard ratio, conditional median difference and geometric-mean ratio accurately. Table S16 summarizes the formal comparisons in the applicable family and their available raw and Holm-Bonferroni-adjusted P values. Shorter recorded ventilation or stay is not automatically favorable because early death can shorten use.

Oxygen exposure. The common website CRF contains scheduled PaO_2 and FIO_2 at 06:00, 12:00, 18:00 and 24:00 with separate daily Lowest and Highest. Scheduled FIO_2 readings and separately recorded daily highest and lowest FIO_2 values apply during ventilation; PaO_2 has no matching ventilation restriction. Duration blocks record SpO_2 ≥97%, SpO_2 <88% and Total SpO_2 Hours; and FIO_2 0.21 hours with Total FIO_2 hours, including after extubation.

Participant percentages will be 100 times summed threshold hours divided by summed corresponding daily totals, using days with both values recorded. Daily percentages will not be averaged. Missing numerators will not be treated as zero, and missing pairs will contribute to neither sum. A zero numerator with a positive total will be included; a percentage will not be calculated for a zero summed total. The daily Highest PaO_2 field will identify values >100 mmHg and the daily Lowest field values <60 mmHg. Each denominator will comprise participants with at least one recorded corresponding extreme.

Participant median percentages and recorded hours will be compared using quantile regression with site-clustered robust standard errors. Binary PaO_2 exposures will be compared using log-binomial models with random site intercepts and the applicable convergence sequence. Exposure tests will be outside the Holm family. Scheduled readings will supply participant daily means, and group means will equally weight contributing participants, with standard errors and daily counts reported. Daily highest and lowest values will use the corresponding separate fields. Values will not be imputed after death or first ICU discharge, or beyond eligible ventilation for ventilated FIO_2 fields. Later-day comparisons will condition on remaining observable; achieved exposure is not itself randomized.

28. Adjustment for covariates

Where stated above, models will adjust for final HIE and non-HIE indicators plus site. Separate diagnostic indicators allow for representation of overlapping conditions.

Supporting primary analyses will add age and sex, followed by baseline covariates with clinically meaningful imbalances. Covariates included because of clinically meaningful imbalances will be selected from summaries for the sepsis population only with treatment allocation masked, before treatment-effect results are examined. The selected variables and their clinical rationale will be documented in the analysis record before fitting the additional model. APACHE II and SAPS 3 are not candidate adjustment covariates because their measurement windows may include post-randomization values; this amends the published illness-severity adjustment.

If models including additional covariates fail, the overarching convergence sequence will apply, with extra covariates omitted one at a time in the order clinically imbalanced variables, age, then sex. Pairs will be omitted in the corresponding order if required. The actual covariates and denominator will be reported. Variable selection will not be based on baseline P values or treatment findings.

29. Sensitivity analyses

The primary models will be repeated among eligible participants and among eligible participants who purposefully received their assigned strategy. Ordinary delivery deviations will not exclude recipients. Reasons and counts will be reported. These analyses will retain randomized allocation and will support the intention-to-treat analysis.

Diagnostic sensitivity 1 will be restricted to unique participants with both an original sepsis-Yes response at randomization and a final sepsis-Yes classification, and permission to use data. Only the first allocation will be used. The primary models and convergence sequence will apply, with final HIE and non-HIE brain-condition indicators and the specified site structure. Cohort membership, deaths and observed denominators will be reported by allocation. Table S14 will present original-versus-final classification and Table S11 will present the sensitivity estimates.

Diagnostic sensitivity 2 will use all unique participants with an original sepsis-Yes response at randomization and permission to use data. This population will include original Yes records subsequently classified as No and exclude original No records subsequently classified as Yes. Membership changes, deaths and denominators will be reported by allocation using the primary model and convergence sequence. Table S14 will present original-versus-final classification.

Diagnostic sensitivity 3 will use the expanded population comprising the final sepsis-Yes cohort together with all participants whose original sepsis response was Yes and final classification was No, subject to permission to use data. This population will retain participants added to the final cohort after an original No response while also restoring original Yes records subsequently classified as No. The primary model and convergence sequence will apply. Cohort membership and overlap with the primary and original-Yes populations will be reported by allocation.

Non-medically-indicated discharge. Two hypothetical analyses will use the contemporaneous recorded flag for ICU discharge to home when ongoing care remained medically indicated. Affected liberal participants will be assigned survival and affected conservative participants death; the second analysis will reverse these assignments. Verified deaths will remain deaths. Flagged participants with missing outcomes will receive the relevant scenario assignment. The primary models will be fitted, and overlap with missing outcomes will be reported. Missing-outcome scenarios and imputation are specified in section 31.

Response-adaptive allocation. The primary models will use inverse-probability-of-treatment weights equal to the reciprocal of each participant's actual probability of receiving the assigned regimen, with categorical randomization epoch included. Epochs will be defined by the dates on which updated randomization probabilities were implemented. For participants with overlapping conditions, the weights will use the probability actually applied under the allocation hierarchy. Risk ratios and risk differences will retain the liberal-versus-conservative orientation.

These sensitivity analyses will be supporting and outside the Holm-Bonferroni family.

30. Subgroup analyses

The two pre-specified factors to be considered in subgroup analyses are: (1) four-category sepsis source: respiratory, gastrointestinal, genitourinary and another source (musculoskeletal/skin, neurologic and other identified sources); and (2) ICU admission following surgery versus not admitted to ICU after surgery [1]. Surgical status will be derived from the surgical-admission Yes/No component of the study-database ICNARC diagnosis code recorded for every participant across all sites.

Main effects and treatment-by-subgroup interactions will be added to the primary risk-ratio model, retaining site and diagnostic adjustment. A single global three-degree-of-freedom sepsis-source interaction and a one-degree-of-freedom surgery interaction will be tested. Events, denominators, subgroup risk ratios and 95% confidence intervals, and interaction P values will be reported regardless of the primary result.

Patients with unknown subgroup values will remain in the primary analysis and will be excluded only from the relevant interaction analysis, with counts reported. The primary convergence sequence will apply where appropriate. Sparse interactions that cannot be estimated will be reported as unavailable

rather than regrouped according to the results. Detailed descriptive categories with fewer than 10 participants may be pooled without changing the four pre-specified sepsis-source categories. Within-subgroup significance comparisons will not be interpreted as heterogeneity; the exploratory interaction tests will be outside the Holm-Bonferroni family.

31. Missing data

Completeness of outcomes, covariates, diagnoses and oxygen measures will be reported by allocation, distinguishing eligible collection denominators from observed analysis denominators. Death or discharge ending physiological collection will not create missing observations afterward. Structural non-collection will be distinguished from sporadic missingness. All-cause day-90 mortality will not be imputed in jurisdictions where it was not collected.

The primary analysis will use observed outcomes. Whenever primary outcomes are missing, one extreme scenario will assign missing liberal outcomes to death and missing conservative outcomes to a non-event; the second scenario will reverse these assignments. The primary models will be fitted in both scenarios. Multiple imputation using 20 datasets will also be performed if either extreme scenario changes the primary inference at the two-sided 5% level, defined as a change between $P<0.05$ and $P\geq0.05$ or a statistically significant finding favoring the opposite strategy. Observed-outcome and imputed estimates will both be reported. No primary-outcome imputation analysis will be performed for a population with complete outcomes.

When multiple imputation is required for this nested trial, suitable imputed datasets from the overarching trial will be reused if available, retaining the relevant Sepsis analysis population and outcome-specific collection population. If suitable overarching-trial imputations are unavailable, 20 imputed datasets will be generated only within the final sepsis-Yes cohort, restricted to the outcome-specific collection population. The first-allocation and data-permission rules will apply. Missing baseline characteristics used in the imputation models will receive the center-specific single mean or, for categorical characteristics, mode substitution specified in the overarching SAP. Baseline characteristics will be compared by outcome availability using t tests or Wilcoxon rank-sum tests for continuous variables and chi-squared tests for categorical variables. These comparisons, the analysis covariates and clinical knowledge will inform the auxiliary predictors; they are not allocation-group baseline balance tests.

For imputation generated within the final sepsis-Yes cohort, outcomes will be imputed separately by allocated group using analysis covariates and relevant baseline predictors of outcome or missingness. Binary outcomes will be imputed using logistic regression without site because of possible perfect prediction in small sites. Continuous-outcome models will include site and use predictive mean matching with five nearest neighbors. 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. When required, ANZ all-cause day-90 mortality will be imputed separately using logistic regression within the final sepsis-Yes cohort intersected with its intended registry-coverage population. No liberation time or structurally uncollected outcome will be imputed.

Imputed distributions will be compared with observed data using proportion plots for binary outcomes and density plots for continuous outcomes where applicable. The pre-specified convergence sequence will apply if a model fails in more than one quarter of imputed datasets. A method will be considered successful when it converges in at least 75% of datasets. The number fitted, omissions and model used will be reported, and available estimates will be combined using Rubin’s rules. An estimate unavailable after the sequence will be reported as unavailable. Secondary clinical outcomes will be analyzed using observed outcomes within their collecting populations. Imputation analyses, when required, will reuse suitable overarching-trial datasets if available; otherwise, they will use the 20 datasets generated within the final sepsis-Yes cohort and the relevant outcome-specific collection population as specified above.

32. Harms

Events were not systematically ascertained. Expected abnormalities, organ failures and critical-illness complications were not routinely reported as serious events. Sites reported events potentially related to intervention or otherwise of concern [1,2,6]. These are reported-event summaries, not the incidence of all complications.

Table S15 will summarize all adverse-event reports recorded for the primary sepsis population under the original Mega-ROX reporting procedures up to database lock. Participant counts, serious reports, total reports, investigator-assessed relatedness and unresolved assessments will be presented by randomized allocation. Each participant will be counted once in participant-based summaries and may contribute multiple reports. The original reporting scope and available event dates will be described with the summary. Safety comparisons will be descriptive; absence of a report will not establish absence of harm.

33. Statistical software and code

Analyses will use Stata version 19 or later or R version 4.4.1 or later, consistent with the overarching SAP. The exact software versions and packages will be recorded. qreg2 will provide site-clustered quantile variance estimates, and Fine–Gray and Cox models will use the specified site-clustered variance estimators. Primary risk models will use binomial log and identity links with the specified site structure.

Illustrative specifications with liberal treatment and conservative reference are

```
xi: gllamm outcome i.TreatmentGroup nonHIE HIE, i(site) fam(binomial) link(log)
xi: gllamm outcome i.TreatmentGroup nonHIE HIE, i(site) fam(binomial) link(identity)
stset survival_time, failure(inhospital_death==1)
stcox i.TreatmentGroup, vce(cluster site)
stcox i.TreatmentGroup nonHIE HIE, vce(cluster site)
stset discharge_time, failure(event_type==1)
stcrreg i.TreatmentGroup nonHIE HIE, compete(event_type==2) vce(cluster site)
qreg2 recorded_duration i.TreatmentGroup nonHIE HIE, cluster(site)
```

Final variable names and syntax will be checked.

The same two trial statisticians described in section 14 will verify primary results, counts and Holm-Bonferroni calculations against the approved plan. The final report will identify material deviations.

34. Modifications from the published SAP

Feasibility changes replace unavailable liberation event-time analysis with completed total ventilation hours, including possible pre-randomization time. Liberation subhazard estimates and CIFs are removed; live ICU/hospital discharge retains competing-risk models. Supporting completed durations will use all available index-episode follow-up, including beyond day 90, and will be distinguished from the formal 90-day discharge event-time analyses. Ongoing episodes at last follow-up will be reported as censored rather than as completed durations.

APACHE II will be summarized descriptively in Table 1 for sites where it was collected and will not be an adjustment covariate. SAPS 3 will remain descriptive for Brazil and will not be an adjustment covariate because its measurement window may extend beyond randomization. Final diagnoses will govern the principal population and adjustment, with concordant original-and-final Yes, original-Yes and expanded-population diagnostic sensitivities. All-site index-hospital survival will remain distinct from ANZ all-cause day-90 mortality.

A comparison in the applicable Holm–Bonferroni family that yields no valid P value will be reported as not estimable and will contribute P=1 solely for multiplicity adjustment. Failure of a supporting Cox model will not invalidate an available formal log-rank test. Observed-outcome analyses and triggered imputation analyses will follow section 31, reusing suitable overarching-trial imputations if available or otherwise generating 20 datasets within the final sepsis-Yes cohort and the relevant outcome-specific collection population. ANZ coverage, representativeness, discharge-flag ascertainment and safety reporting will follow the populations and procedures defined in this SAP. The report will document the

analysis denominators and the dates of SAP approval, public posting, database lock and access to treatment results.

Alignment with the overarching SAP version 2.0 dated 9 November 2026 clarifies data-source selection, allocation-masked selection of additional covariates, implementation-date randomization epochs and reuse of suitable overarching-trial imputations if available, with imputation within the final sepsis-Yes cohort and relevant outcome-specific collection population otherwise. Table S2 will report all governing diagnostic groups represented in the sepsis cohort, and Table S10 will apply the common purposeful-receipt definitions.

35. References

1. Young PJ et al. Protocol and statistical analysis plan for Mega-ROX Sepsis. Critical Care and Resuscitation. 2023;25:106–112. doi:10.1016/j.ccrj.2023.04.008.

2. Kasza J and Young PJ. Mega-ROX overarching detailed statistical analysis plan. Version 2.0 dated 9 November 2026.

3. Young PJ, Arabi YM, Bagshaw SM et al. Protocol and statistical analysis plan for the Mega-ROX research program. Critical Care and Resuscitation. 2022;24:137–149. doi:10.51893/2022.2.OA4.

4. Kasza J and Young PJ. LOGICAL detailed statistical analysis plan. Final version dated 14 November 2025.

5. Singer M et al. The Third International Consensus Definitions for Sepsis and Septic Shock Sepsis-3. JAMA. 2016;315:801–810. doi:10.1001/jama.2016.0287.

6. Cook D et al. Serious adverse events in academic critical care research. CMAJ. 2008;178:1181–1184. doi:10.1503/cmaj.071366.

36. Appendix planned tables and figures

Ratios will compare liberal with conservative oxygen, and differences will be liberal minus conservative. The tables and figures will present the planned analyses with the outcome-specific populations and denominators described in this SAP.

Table 1: Characteristics of the Patients at Baseline*

Characteristic	Liberal oxygen (n=XXX)	Conservative 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)
APACHE II score§	xx.x ± xx	xx.x ± xx
SAPS 3 score¶	xx.x ± xx	xx.x ± xx
Sepsis source – no. (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Genitourinary	xxx (xx.x)	xxx (xx.x)
Musculoskeletal and skin	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)
COVID-19 – no. (%)	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 expressed as mean ± SD.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Clinical Frailty Scale include 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill). Patients were evaluated according to their condition before the current admission.
§ APACHE II scores range from 0 to 71, with higher scores indicating more severe illness.
¶ Scores on the SAPS 3 range from 0 to 217, with higher scores indicating more severe disease. The SAPS 3 score was collected from trial participants from Brazil.
Abbreviations: APACHE II: Acute Physiology and Chronic Health Evaluation II; 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; SD: standard deviation.

Table 2: Oxygen Exposure Metrics*				
Oxygen exposure metric	Liberal oxygen (n=XXX)	Conservative oxygen (n=XXX)	Difference† (95% CI)	Risk ratio‡ (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 (%)	[n/N (%)]	[n/N (%)]		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 (%)	[n/N (%)]	[n/N (%)]		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)	

* Data cover eligible CRF day labels 0–7 until collection ends, death or first ICU discharge. Each metric reports its contributing participant count. Percentages sum recorded threshold hours over matching recorded total hours, rather than average daily percentages. Zero threshold hours with positive totals are retained; a missing numerator is not zero.

† Differences in medians use quantile regression with site-clustered robust standard errors, liberal minus conservative; percentages are in percentage points. ‡ Binary risks use log-binomial regression with random site intercepts and the overarching convergence sequence. Daily Highest and Lowest PaO_2 fields define the >100 and <60 mmHg events. Intervals are pointwise and exposure comparisons are outside the secondary Holm family.

Table 3: Primary and Secondary Outcomes*			
Outcome	Liberal oxygen N=[N]	Conservative oxygen N=[N]	Estimate (95% CI)
Primary outcome			
Death during the index hospitalization within 90 days, no. (%)	[n/N (%)]	[n/N (%)]	Risk ratio [X.XX; 95% CI]† Risk difference [X.X percentage points; 95% CI]
Secondary outcomes			
Completed total invasive ventilation hours‡			
Number with recorded completed duration	[N]	[N]	
Median (IQR), hours	[median (IQR)]	[median (IQR)]	Conditional median difference [hours; 95% CI]‡
Days to live ICU discharge‡			
Number of patients	[N events]	[N events]	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subdistribution HR [95% CI]‡
Days to live hospital discharge‡			
Number of patients	[N events]	[N events]	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subdistribution HR [95% CI]‡
Discharged directly home from hospital, no. (%)	[n/N (%)]	[n/N (%)]	Risk ratio [X.XX; 95% CI]§ Risk difference [X.X percentage points; 95% CI]
Survival during the index hospitalization, deaths/N	[deaths/N]	[deaths/N]	[Hazard ratio; 95% CI]¶

* Primary P=[P] is from the risk-ratio model. All 95% confidence intervals are pointwise. Table S16 gives the secondary raw and Holm-adjusted P values. Table S12 gives ANZ all-cause day-90 mortality if the death registry linkage requirement in Section 27 is met.

† Log-binomial risk ratios and separate identity-link risk differences will adjust for final HIE and non-HIE brain-condition indicators and a random site intercept, following the overarching convergence sequence. Risk differences will be liberal minus conservative in percentage points.

‡ Total ventilation hours will include any pre-randomization hours and hours before death and will be compared using adjusted quantile regression with site-clustered standard errors. Fine–Gray models for live ICU/hospital exit will adjust for the same diagnoses with site-clustered errors and death competing. A CIF median will be reported only if live discharge reaches 50%. § Direct-home analyses will exclude SA001 and retain SA002; missing destination will remain missing. ¶ Survival will be compared using the log-rank test with supporting Cox models; follow-up will be censored at live index-hospital exit, day 90 or the last reliable observation.

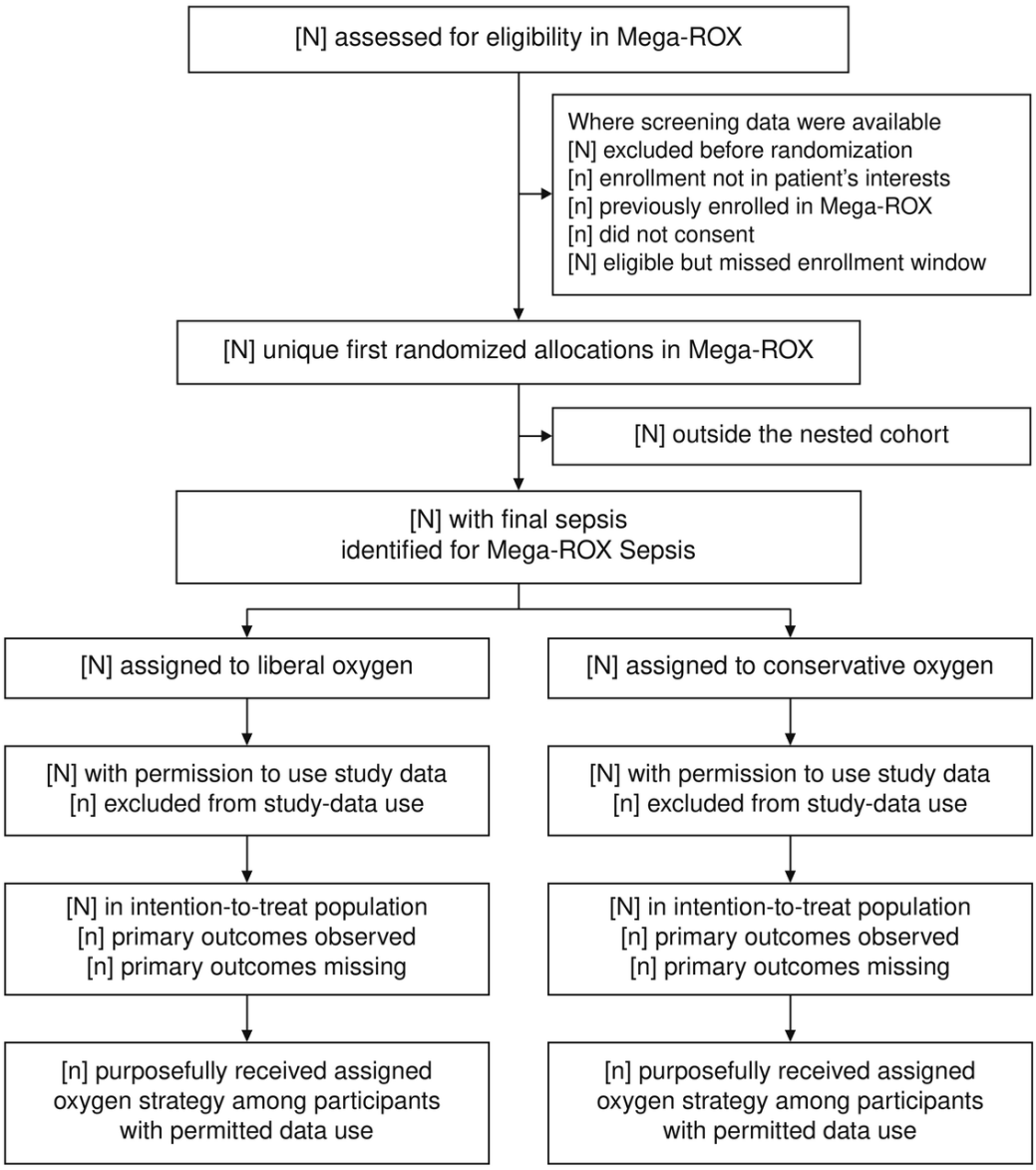


Figure 1. Randomization and Follow-up.
The figure will describe screening in Mega-ROX, identification of the final sepsis cohort, first allocations, data-use exclusions, and primary-outcome availability. Purposeful receipt of the assigned strategy is reported among participants with permitted data use. Membership outside the sepsis cohort will not by itself exclude a participant from the overarching analysis.

Mega-ROX Sepsis denotes the nested trial; HIE denotes hypoxic ischemic encephalopathy. Final diagnostic categories determine the main cohort; original classifications are examined separately.

PANEL A Survival during the index hospitalization

Kaplan–Meier curves will be presented by randomized allocation.
The x-axis will show days 0, 15, 30, 45, 60, 75 and 90 after randomization; the y-axis will show survival probability from 0 to 1.
Numbers at risk will be shown at each time point.
Unadjusted and adjusted Cox hazard ratios with 95% CIs and raw and Holm-adjusted log-rank P values will be presented.

PANEL B Pre-specified subgroup analyses

A forest plot will show the mortality risk ratios for respiratory, gastrointestinal, genitourinary and other sources of sepsis, and ICU admission following surgery versus not admitted to ICU after surgery.
Risk ratios will be presented with 95% CIs, event counts and denominators.
The sepsis-source and admission-following-surgery interaction P values will be presented; separate within-subgroup significance tests are not planned.

Figure 2. Survival during the Index Hospitalization and Pre-specified Subgroup Analyses.
Panel A censors at live discharge or transfer from the index hospital, day 90 or last reliable in-hospital observation. It does not estimate complete 90-day all-cause survival. Panel B presents risk ratios for mortality during the index hospitalization within 90 days, liberal relative to conservative oxygen. Values below 1 favor liberal oxygen. Diagnostic adjustment uses final HIE and non-HIE brain condition indicators. Confidence intervals are pointwise. Subgroup interaction tests are exploratory.

PANEL A Recorded total invasive ventilation hours The distribution of completed total ventilation hours will be presented by randomized allocation. The x-axis will show completed total ventilation hours during the index ICU episode; the y-axis will show the cumulative proportion from 0 to 1. Observed medians and IQRs and the adjusted conditional median difference with a 95% CI will be presented. Zero-hour observations will be retained.
PANEL B Live ICU discharge and competing death Cumulative incidence functions will show live ICU discharge and competing death for each randomized allocation. The x-axis will show days 0, 15, 30, 45, 60, 75 and 90 after randomization; the y-axis will show cumulative incidence from 0 to 100%. Numbers at risk and the Fine–Gray live-discharge subdistribution hazard ratio with its 95% CI will be presented.
PANEL C Live hospital discharge and competing death Cumulative incidence functions will show live hospital discharge and competing death for each randomized allocation. The x-axis will show days 0, 15, 30, 45, 60, 75 and 90 after randomization; the y-axis will show cumulative incidence from 0 to 100%. Numbers at risk and the Fine–Gray live-discharge subdistribution hazard ratio with its 95% CI will be presented.
Figure 3. Recorded Ventilation Duration and Cumulative Incidence of Live Discharge. Panel A displays completed total ventilation hours, including any pre-randomization hours and hours before death. Panels B and C show live exit from the index ICU and hospital with death competing. Liberal-to-conservative subdistribution hazard ratios above 1 indicate greater live-discharge incidence. A CIF median is reported only if live discharge reaches 50%; otherwise it is not reached. Later readmission does not extend the index episode.

37. Supplementary tables

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.

For this nested trial, ventilation and direct-home analyses will exclude SA001 and retain SA002. Structural non-collection will not be imputed; all-cause day-90 mortality analyses retain the predefined ANZ registry-coverage population.

Table S2: Randomization Ratios Applied in the Mega-ROX Sepsis Trial

Allocation epoch (start date)	Trial IDs	Hierarchy for overlapping diagnoses	Liberal:conservative ratios by governing diagnostic group
Initial allocation [date]	[1–n]	Hypoxic ischemic encephalopathy, then sepsis, and then other brain conditions.	HIE: [ratio] Sepsis: 1.05:1 Other brain condition: [ratio] None: [ratio]
After 1,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 8,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 16,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 24,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 32,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]

Allocation records will provide the implementation dates, trial-ID boundaries, hierarchy and ratios for each epoch and governing diagnostic group represented in the sepsis cohort. Each participant's actual allocation probability, accounting for overlapping diagnoses and the hierarchy applied at randomization, will be used for weighting. The sepsis cohort includes participants whose allocation probability was governed by another diagnostic group. Ratios in this table are liberal to conservative; the initial sepsis ratio of 1.05:1 therefore favored liberal oxygen.

Table S3: Pre-specified Oxygen Exposure Metrics	
Outcome	Method of ascertainment*
Physiological outcomes	
The proportion of hours in ICU over CRF day labels 0–7 when the SpO_2 was ≥97%.	Each participant's percentage will be 100 × the sum of recorded daily SpO_2 ≥97% hours divided by the sum of corresponding daily Total SpO_2 Hours, using days with both numerator and denominator recorded. Positive total hours will be required; daily percentages will not be averaged.
The total number of hours in ICU over CRF day labels 0–7 when the SpO_2 was ≥97%.	Recorded daily SpO_2 ≥97% hours will be summed over the same eligible paired days as the percentage metric. Missing hours will not be assigned zero.
The proportion of hours in ICU over CRF day labels 0–7 when the SpO_2 was <88%.	Each participant's percentage will be 100 × the sum of recorded daily SpO_2 <88% hours divided by the sum of corresponding daily Total SpO_2 Hours, using days with both numerator and denominator recorded. Positive total hours will be required; daily percentages will not be averaged.
The total number of hours in ICU over CRF day labels 0–7 when the SpO_2 was <88%.	Recorded daily SpO_2 <88% hours will be summed over the same eligible paired days as the percentage metric. Missing hours will not be assigned zero.
Mean daily PaO_2 in ICU over CRF day labels 0–7	Each participant's daily mean PaO_2 will be calculated from the available scheduled 06:00, 12:00, 18:00 and 24:00 readings. PaO_2 has no corresponding ventilation restriction. Group summaries will weight participants equally and report standard errors and contributing participant counts.
Highest daily PaO_2 in ICU over CRF day labels 0–7	The separately recorded daily Highest PaO_2 field will define this measure. Extrema of the scheduled readings will not be substituted. Group means, standard errors and contributing participant counts will be reported.
Lowest daily PaO_2 in ICU over CRF day labels 0–7	The separately recorded daily Lowest PaO_2 field will define this measure. Extrema of the scheduled readings will not be substituted. Group means, standard errors and contributing participant counts will be reported.
Process measures	
The proportion of hours in ICU over CRF day labels 0–7 when the FIO_2 was 0.21	Each participant's percentage will be 100 × the sum of recorded daily FIO_2 =0.21 hours divided by the sum of corresponding daily Total FIO_2 Hours, using days with both numerator and denominator recorded. Positive total hours will be required; daily percentages will not be averaged.
The total number of hours in ICU over CRF day labels 0–7 when the FIO_2 was 0.21	Recorded daily FIO_2 =0.21 hours will be summed over the same eligible paired days as the percentage metric. Missing hours will not be assigned zero. The FIO_2 duration block includes ventilation and the period after extubation.
Mean daily FIO_2 (while ventilated) over CRF day labels 0–7	Each participant's daily mean FIO_2 will be calculated from the available scheduled 06:00, 12:00, 18:00 and 24:00 readings while invasively ventilated. Group summaries will weight participants equally and report standard errors and contributing participant counts.
Highest daily FIO_2 (while ventilated) over CRF day labels 0–7	The separately recorded daily Highest FIO_2 field while invasively ventilated will define this measure. Extrema of the scheduled readings will not be substituted. Group means, standard errors and contributing participant counts will be reported.
Lowest daily FIO_2 (while ventilated) over CRF day labels 0–7	The separately recorded daily Lowest FIO_2 field while invasively ventilated will define this measure. Extrema of the scheduled readings will not be substituted. Group means, standard errors and contributing participant counts will be reported.

* Collection ends at the recorded end, death or first ICU discharge, whichever occurs first. Eligible ventilation additionally defines ventilated FIO_2 fields. CRF day labels 0–7 do not imply eight complete days or a fixed 168-hour denominator. Threshold PaO_2 events use the corresponding daily Highest or Lowest field and participants with at least one value in that field.

Table S4: Causes of Respiratory Sepsis		
Sepsis source	Liberal oxygen (n=[N])	Conservative oxygen (n=[N])
Respiratory sepsis – n (%)		
Respiratory sinus infection	xxx (xx.x)	xxx (xx.x)
Tonsil or pharyngeal infection	xxx (xx.x)	xxx (xx.x)
Epiglottitis	xxx (xx.x)	xxx (xx.x)
Pertussis	xxx (xx.x)	xxx (xx.x)
Croup or laryngotracheobronchitis (non-influenza)	xxx (xx.x)	xxx (xx.x)
Acute bronchitis, non-influenza	xxx (xx.x)	xxx (xx.x)
Infective exacerbation of COPD	xxx (xx.x)	xxx (xx.x)
Bronchiectasis	xxx (xx.x)	xxx (xx.x)
Bacterial pneumonia	xxx (xx.x)	xxx (xx.x)
Viral pneumonia, non-influenza (including COVID-19)	xxx (xx.x)	xxx (xx.x)
Influenza	xxx (xx.x)	xxx (xx.x)
Fungal or yeast pneumonia	xxx (xx.x)	xxx (xx.x)
Parasitic pneumonia	xxx (xx.x)	xxx (xx.x)
Pneumonia, no organism isolated	xxx (xx.x)	xxx (xx.x)
Lung abscess	xxx (xx.x)	xxx (xx.x)
Tuberculosis	xxx (xx.x)	xxx (xx.x)
Empyema or infected effusion	xxx (xx.x)	xxx (xx.x)
Pleurisy	xxx (xx.x)	xxx (xx.x)

Abbreviations: COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019.

Table S5: Causes of Gastrointestinal Sepsis		
Sepsis source	**Liberal oxygen (n=[N])**	**Conservative oxygen (n=[N])**
Gastrointestinal sepsis – n (%)	xxx (xx.x)	xxx (xx.x)
Infective esophagitis	xxx (xx.x)	xxx (xx.x)
Infective enteritides	xxx (xx.x)	xxx (xx.x)
Necrotizing enterocolitis	xxx (xx.x)	xxx (xx.x)
Appendicitis or appendiceal abscess	xxx (xx.x)	xxx (xx.x)
Diverticulitis or diverticular abscess	xxx (xx.x)	xxx (xx.x)
Infective colitis or proctocolitis	xxx (xx.x)	xxx (xx.x)
Infective hepatitis	xxx (xx.x)	xxx (xx.x)
Infective cholangitis	xxx (xx.x)	xxx (xx.x)
Hepatic abscess	xxx (xx.x)	xxx (xx.x)
Hydatid disease	xxx (xx.x)	xxx (xx.x)
Acute cholecystitis or empyema of gall bladder	xxx (xx.x)	xxx (xx.x)
Gangrenous gall bladder	xxx (xx.x)	xxx (xx.x)
Pancreatic abscess or infected pseudocyst	xxx (xx.x)	xxx (xx.x)
Infective pancreatitis	xxx (xx.x)	xxx (xx.x)
Primary peritonitis	xxx (xx.x)	xxx (xx.x)
Intra-peritoneal abscess (not pelvic)	xxx (xx.x)	xxx (xx.x)
CAPD related peritonitis	xxx (xx.x)	xxx (xx.x)
Pelvic infection or abscess	xxx (xx.x)	xxx (xx.x)
Retroperitoneal abscess or infection	xxx (xx.x)	xxx (xx.x)
Tuberculous peritonitis	xxx (xx.x)	xxx (xx.x)

Abbreviations: CAPD: continuous ambulatory peritoneal dialysis.

Table S6: Causes of Genitourinary Sepsis		
Sepsis source	**Liberal oxygen (n=[N])**	**Conservative oxygen (n=[N])**
Genitourinary sepsis – n (%)	xxx (xx.x)	xxx (xx.x)
Pyelonephritis or pyonephrosis	xxx (xx.x)	xxx (xx.x)
Perinephric abscess	xxx (xx.x)	xxx (xx.x)
Cystitis, pyocystis or urethritis	xxx (xx.x)	xxx (xx.x)
Uterine cavity infection	xxx (xx.x)	xxx (xx.x)
Pelvic infection or abscess	xxx (xx.x)	xxx (xx.x)
Toxic shock syndrome	xxx (xx.x)	xxx (xx.x)
Tubo-ovarian abscess	xxx (xx.x)	xxx (xx.x)
Amnionitis	xxx (xx.x)	xxx (xx.x)
Infected retained products of conception	xxx (xx.x)	xxx (xx.x)
Septic abortion	xxx (xx.x)	xxx (xx.x)
Prostatitis	xxx (xx.x)	xxx (xx.x)
Testicular, prostatic or penile abscess	xxx (xx.x)	xxx (xx.x)

Table S7: Causes of Musculoskeletal and Skin Sepsis		
Sepsis source	**Liberal oxygen (n=[N])**	**Conservative oxygen (n=[N])**
Musculoskeletal and skin sepsis – n (%)	xxx (xx.x)	xxx (xx.x)
Discitis	xxx (xx.x)	xxx (xx.x)
Spinal osteomyelitis or vertebral abscess	xxx (xx.x)	xxx (xx.x)
Osteomyelitis of the pelvis or long bones	xxx (xx.x)	xxx (xx.x)
Infective arthritis	xxx (xx.x)	xxx (xx.x)
Infected joint prosthesis	xxx (xx.x)	xxx (xx.x)
Myositis	xxx (xx.x)	xxx (xx.x)
Necrotizing fasciitis	xxx (xx.x)	xxx (xx.x)
Rhabdomyolysis	xxx (xx.x)	xxx (xx.x)
Muscle or connective tissue abscess	xxx (xx.x)	xxx (xx.x)
Fournier's gangrene of abdominal wall	xxx (xx.x)	xxx (xx.x)
Fournier's gangrene of perineal tissues	xxx (xx.x)	xxx (xx.x)
Sternotomy related infection	xxx (xx.x)	xxx (xx.x)
Device related abdominal wall infection	xxx (xx.x)	xxx (xx.x)
Cutaneous cellulitis	xxx (xx.x)	xxx (xx.x)
Pressure injury, ulcers or sores	xxx (xx.x)	xxx (xx.x)

Table S8: Other Causes of Sepsis		
Sepsis source	**Liberal oxygen (n=[N])**	**Conservative oxygen (n=[N])**
Infection present but not specified as the primary reason for ICU admission – n (%)	xxx (xx.x)	xxx (xx.x)
Cardiovascular system sepsis – n (%)	xxx (xx.x)	xxx (xx.x)
Viral or bacterial cardiomyopathy	xxx (xx.x)	xxx (xx.x)
Myocardial or septal abscess	xxx (xx.x)	xxx (xx.x)
Myocarditis	xxx (xx.x)	xxx (xx.x)
Non-valvular endocarditis	xxx (xx.x)	xxx (xx.x)
Infective pericarditis	xxx (xx.x)	xxx (xx.x)
Endocarditis, aortic root abscess, prosthetic heart valve infection, infected thoracic aortic prosthesis	xxx (xx.x)	xxx (xx.x)
Infected artificial pacemaker	xxx (xx.x)	xxx (xx.x)
Syphilitic aortitis	xxx (xx.x)	xxx (xx.x)
Infected thrombophlebitis of the great veins	xxx (xx.x)	xxx (xx.x)
Infected intravenous catheter in the great veins	xxx (xx.x)	xxx (xx.x)
Infected thrombophlebitis of the peripheral veins	xxx (xx.x)	xxx (xx.x)
Infected intravenous catheter in the peripheral veins	xxx (xx.x)	xxx (xx.x)
Infected arterio-venous shunt or fistula	xxx (xx.x)	xxx (xx.x)
Infected abdominal aortic prosthesis	xxx (xx.x)	xxx (xx.x)
Infected iliac prosthesis	xxx (xx.x)	xxx (xx.x)
Neurological system sepsis – n (%)	xxx (xx.x)	xxx (xx.x)
Meningitis, unspecified	xxx (xx.x)	xxx (xx.x)
Encephalitis	xxx (xx.x)	xxx (xx.x)
Intracranial abscess	xxx (xx.x)	xxx (xx.x)
Infected CSF shunt	xxx (xx.x)	xxx (xx.x)
Meningococcal meningitis	xxx (xx.x)	xxx (xx.x)
Bacterial meningitis, not meningococcal	xxx (xx.x)	xxx (xx.x)
Viral meningitis	xxx (xx.x)	xxx (xx.x)
Tuberculous meningitis	xxx (xx.x)	xxx (xx.x)
Epidural or subdural spinal infection	xxx (xx.x)	xxx (xx.x)
Poliomyelitis	xxx (xx.x)	xxx (xx.x)
Tetanus	xxx (xx.x)	xxx (xx.x)
Infective polyneuropathy	xxx (xx.x)	xxx (xx.x)
Leprosy	xxx (xx.x)	xxx (xx.x)
Botulism	xxx (xx.x)	xxx (xx.x)
Miscellaneous sepsis – n (%)	xxx (xx.x)	xxx (xx.x)
Leishmaniasis	xxx (xx.x)	xxx (xx.x)
Malaria	xxx (xx.x)	xxx (xx.x)
HIV	xxx (xx.x)	xxx (xx.x)
Septicemia	xxx (xx.x)	xxx (xx.x)
Mononucleosis	xxx (xx.x)	xxx (xx.x)
Leptospirosis	xxx (xx.x)	xxx (xx.x)
Mediastinitis	xxx (xx.x)	xxx (xx.x)
Mandible, facial bones, dental or salivary infection	xxx (xx.x)	xxx (xx.x)
Orbital cellulitis	xxx (xx.x)	xxx (xx.x)
Mastoid infection	xxx (xx.x)	xxx (xx.x)

Table S9: Representativeness of the Trial Participants*		
Characteristic	**ANZ trial cohort**	**ANZ registry reference cohort**
Age, years — mean (SD)	[summary; observed N]	[summary; observed N]
Male sex — n/N (%)	[summary; observed N]	[summary; observed N]
Source of ICU admission — n/N (%)	[summary; observed N]	[summary; observed N]
Emergency department	[summary; observed N]	[summary; observed N]
Hospital ward	[summary; observed N]	[summary; observed N]
Another ICU	[summary; observed N]	[summary; observed N]
Another hospital, excluding ICU	[summary; observed N]	[summary; observed N]
Operating theater following surgery	[summary; observed N]	[summary; observed N]

The comparison will use ANZ trial participants and adult ANZICS Adult Patient Database admissions with recorded sepsis and unplanned invasive ventilation at participating ICUs during the same recruitment periods. Eligibility matching and characteristics will be restricted to features observable in both sources. Observed and missing denominators will be reported for each characteristic. The comparison will be descriptive, without baseline significance tests, and will apply only to this ANZ registry reference population.

Table S10: Protocol Deviations and Delivery of Allocated Treatment*		
Nature of deviation	**Liberal oxygen (n=[N])**	**Conservative oxygen (n=[N])**
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		
FIO2 greater than 0.21 and not reduced when the SpO2 was 95% or more	Not applicable	xxx (xx.x)
Used an FIO2 less than 0.3 during mechanical ventilation	xxx (xx.x)	Not applicable

* Receipt requires purposeful implementation at some point; initially withheld treatment later implemented counts as received. Eligibility and receipt are separate. Deviation categories may overlap.
Abbreviations: FIO2, fraction of inspired oxygen; ICU, intensive care unit; PaO2, arterial partial pressure of oxygen; SaO2, arterial oxygen saturation; SpO2, oxygen saturation measured by peripheral pulse oximetry.

Table S11: Additional Analyses of Primary and Secondary Outcomes*

	Liberal oxygen (n=XXX)	Conservative oxygen (n=XXX)	Risk difference, median difference or geometric-mean ratio† (95% CI)	Relative risk (95% CI)
Death during the index hospitalization within 90 days				
Primary observed-outcome intention-to-treat analysis	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Additional adjustment for age and sex	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Additional adjustment for age, sex and clinically meaningful imbalances	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Eligible participants only	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Eligible participants who purposefully received their assigned strategy	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Inverse-probability weighted analysis with categorical randomization epoch	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Missing outcomes: liberal dead, conservative alive	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Missing outcomes: liberal alive, conservative dead	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Multiple imputation using 20 datasets, if triggered	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Non-medically-indicated discharge: liberal dead, conservative alive	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Non-medically-indicated discharge: liberal alive, conservative dead	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Diagnostic sensitivity 1: original Yes and final Yes population	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Diagnostic sensitivity 2: original randomization sepsis Yes population	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Diagnostic sensitivity 3: expanded final cohort plus original-Yes/final-No participants	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Secondary completed-duration analyses				
Completed ICU duration, median (IQR), days	[median (IQR)]	[median (IQR)]	[Conditional median difference; 95% CI]	—
Completed hospital duration, median (IQR), days	[median (IQR)]	[median (IQR)]	[Conditional median difference; 95% CI]	—
Geometric mean total invasive ventilation duration, hours (95% CI)	[GM; 95% CI]	[GM; 95% CI]	[GMR; 95% CI]	
Geometric mean total invasive ventilation duration in survivors, hours (95% CI)	[GM; 95% CI]	[GM; 95% CI]	Descriptive	
Geometric mean total invasive ventilation duration in non-survivors, hours (95% CI)	[GM; 95% CI]	[GM; 95% CI]	Descriptive	
Geometric mean ICU duration, days (95% CI)	[GM; 95% CI]	[GM; 95% CI]	[GMR; 95% CI]	
Geometric mean ICU duration in survivors, days (95% CI)	[GM; 95% CI]	[GM; 95% CI]	Descriptive	
Geometric mean ICU duration in non-survivors, days (95% CI)	[GM; 95% CI]	[GM; 95% CI]	Descriptive	
Geometric mean hospital duration, days (95% CI)	[GM; 95% CI]	[GM; 95% CI]	[GMR; 95% CI]	
Geometric mean hospital duration in survivors, days (95% CI)	[GM; 95% CI]	[GM; 95% CI]	Descriptive	
Geometric mean hospital duration in non-survivors, days (95% CI)	[GM; 95% CI]	[GM; 95% CI]	Descriptive	

* Primary sensitivities will retain log-link risk-ratio and separate identity-link risk-difference models with random site intercepts and final HIE and non-HIE brain-condition indicators. The model, population and denominator will be reported for each analysis. If either extreme missing-outcome scenario changes the primary 5% inference or reverses a statistically significant direction, the final sepsis-Yes cohort will be analyzed using 20 imputed datasets, reusing suitable overarching-trial imputations if available or otherwise generating them within that cohort as specified in section 31. Diagnostic populations will follow section 29.

† Completed ICU and hospital durations will also be compared using adjusted quantile regression; the treatment coefficient is the liberal-minus-conservative conditional median difference in days. Positive completed durations will be compared using log-linear geometric-mean ratios, diagnostic adjustment and site-clustered standard errors. Ventilation will be measured in hours; ICU/hospital durations will be measured in days from randomization to the recorded episode end or death, using all available follow-up, including beyond day 90. Ongoing episodes will be right-censored at last available follow-up and will not enter completed-duration models as completed values. Completed, censored and missing-duration counts will be reported by allocation for each stay outcome (Table S13). Zero durations will be reported separately and retained in quantile analyses. Survival strata will be descriptive. Ratios will compare liberal with conservative oxygen; risk differences will be liberal minus conservative. APACHE II and SAPS 3 will not be adjustment covariates. Confidence intervals will be pointwise. GM denotes geometric mean; GMR, ratio of geometric means.

Table S12: All-Cause Mortality by Day 90 in the ANZ Registry-Coverage Population		
Measure	Liberal oxygen	Conservative oxygen
Eligible ANZ participants	[N]	[N]
Registry-linked participants	[n/N (%)]	[n/N (%)]
Deaths by day 90, including after discharge	[n/N (%)]	[n/N (%)]
Unknown day-90 vital status	[n/N (%)]	[n/N (%)]
Adjusted risk ratio (95% CI)	[RR (95% CI)]	Reference
Adjusted risk difference, percentage points (95% CI)	[RD (95% CI)]	Reference

The raw P value for the adjusted risk-ratio comparison is [P]. Include the Holm-adjusted P value [adjusted P] only if this outcome is part of the primary manuscript's Holm family.

The ANZ all-cause mortality analysis will use the registry-coverage population defined in sections 20 and 26 and the common binary-outcome models. Live hospital discharge alone will not establish survival through day 90. Coverage, linkage and outcome denominators will be reported separately. No outcome will be imputed in a jurisdiction where it was not collected. Reporting of ANZ all-cause day-90 mortality is subject to the death registry linkage requirement in Section 27.

Table S13: Outcome Availability by Randomized Allocation		
Outcome	Liberal oxygen	Conservative oxygen
In-hospital mortality within 90 days	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]
Survival event date and censoring	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]
Live ICU discharge	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]
Live hospital discharge	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]
Completed total invasive ventilation hours	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]
Supporting completed ICU duration	[eligible N; completed n; right-censored n; missing n]	[eligible N; completed n; right-censored n; missing n]
Supporting completed hospital duration	[eligible N; completed n; right-censored n; missing n]	[eligible N; completed n; right-censored n; missing n]
Direct discharge home	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]
ANZ all-cause day-90 mortality	[eligible N; observed n; missing n]	[eligible N; observed n; missing n]

Structural non-collection, incomplete linkage, missing status, missing event time and administrative censoring will be reported separately. A known death status will be retained when the exact event time is unavailable. Use of the midday discharge-time convention will be reported separately. Endpoint-specific denominators will not redefine the intention-to-treat population. Supporting ICU and hospital durations will distinguish completed episodes (including those ending after day 90), ongoing episodes right-censored at last follow-up, and missing completed durations.

Table S14: Original and Final Diagnostic Classifications		
Classification	**Liberal oxygen**	**Conservative oxygen**
Original Yes; final Yes	[n]	[n]
Original Yes; final No	[n]	[n]
Original No; final Yes	[n]	[n]
Original No; final No	[n]	[n]

The classification matrix will include unique parent-trial participants with permission to use study data, including participants outside the final sepsis cohort. Original and final sepsis classifications are complete Yes/No variables. Each nested analysis will retain its own denominator. Cohort counts and primary-outcome sensitivity estimates will be presented in Table S11.

Table S15: Reported Adverse Events		
Measure	Liberal oxygen	Conservative oxygen
Participants with at least one reported adverse event	[n/N (%)]	[n/N (%)]
Total adverse-event reports	[n]	[n]
Participants with a serious report	[n/N (%)]	[n/N (%)]
Total serious reports	[n]	[n]
Reports assessed as potentially related	[n]	[n]
Unresolved relatedness or seriousness	[n]	[n]
[Reported event category]	[participants n; reports n]	[participants n; reports n]

These summaries will describe reported events rather than systematic ascertainment of every complication. Participant counts and report totals will be presented separately using the recorded event categories, seriousness, relatedness and original reporting scope. Event reports available up to database lock will contribute to the summary.

Table S16: Secondary Comparisons and Multiplicity				
Outcome	Formal comparison	Raw P	Adjusted P	Supporting estimate
Survival during index hospitalization	Log-rank	[P]	[Holm-adjusted P]	[supporting Cox HR; 95% CI]
Live ICU discharge	Fine–Gray treatment test	[P]	[Holm-adjusted P]	[subdistribution HR; 95% CI]
Live hospital discharge	Fine–Gray treatment test	[P]	[Holm-adjusted P]	[subdistribution HR; 95% CI]
Completed total ventilation hours	Quantile-regression treatment test	[P]	[Holm-adjusted P]	[median difference; 95% CI]
Direct discharge home	Log-binomial treatment test	[P]	[Holm-adjusted P]	[RR; 95% CI]
ANZ all-cause day-90 mortality	Log-binomial treatment test	[P]	[Holm-adjusted P]	[RR; 95% CI]

Section 17 specifies the applicable Holm–Bonferroni family. If ANZ all-cause day-90 mortality reporting is deferred, omit its row and adjust the other five outcomes. Raw and adjusted P values will be reported for each estimable comparison. 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 and its result displayed 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 log-rank test. Supporting Cox, duration, geometric-mean, exposure, sensitivity and interaction analyses will be outside this family. Confidence intervals will be ordinary pointwise 95% intervals.

38. Supplementary figures

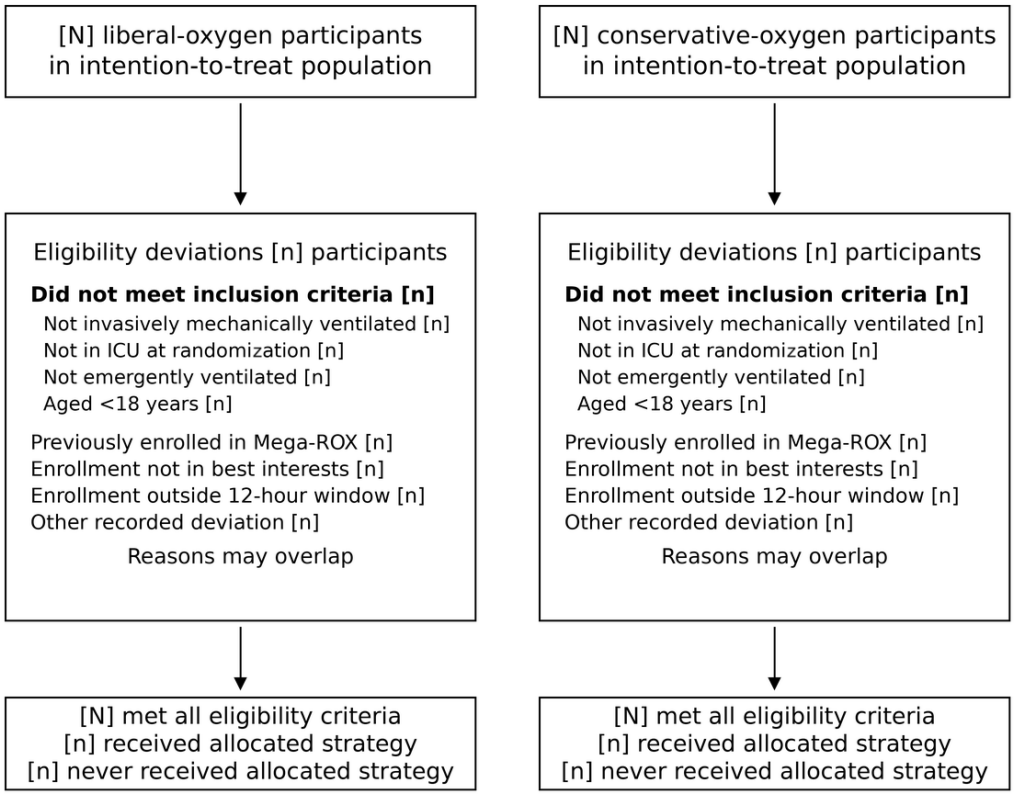


Figure S1. Protocol Deviations Affecting Trial Eligibility.
Participants and recorded reasons are summarized by randomized allocation. Reasons may overlap. Failure to receive treatment is classified separately from eligibility.

Mega-ROX Sepsis denotes the nested trial. This figure is descriptive; the primary intention-to-treat population retains participants with eligibility deviations.

PANEL A Mean daily FIO_2 by randomized allocation

Group means and standard errors will be shown at CRF day labels 0–7, with contributing participant counts. The x-axis will show CRF days and the y-axis will show FIO_2 as a fraction from 0.21 to 1.00. Each participant will contribute one value to each daily measure.

PANEL B Highest daily FIO_2 by randomized allocation

Group means and standard errors will be shown at CRF day labels 0–7, with contributing participant counts. The x-axis will show CRF days and the y-axis will show FIO_2 as a fraction from 0.21 to 1.00. Each participant will contribute one value to each daily measure.

PANEL C Lowest daily FIO_2 by randomized allocation

Group means and standard errors will be shown at CRF day labels 0–7, with contributing participant counts. The x-axis will show CRF days and the y-axis will show FIO_2 as a fraction from 0.21 to 1.00. Each participant will contribute one value to each daily measure.

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 recordings; panels B and C use the separately recorded daily Highest and Lowest fields. Group summaries weight participants equally. FIO2 values apply while invasively ventilated. Observations end at recorded end of collection, death or first ICU discharge, as applicable. Day labels do not imply eight complete observation days. Later-day summaries condition on remaining observable; missing values are not filled. No repeated-measures treatment P value is planned.

PANEL A Mean daily PaO_2 by randomized allocation

Group means and standard errors will be shown at CRF day labels 0–7, with contributing participant counts. The x-axis will show CRF days and the y-axis will show PaO_2 in mmHg. Each participant will contribute one value to each daily measure.

PANEL B Highest daily PaO_2 by randomized allocation

Group means and standard errors will be shown at CRF day labels 0–7, with contributing participant counts. The x-axis will show CRF days and the y-axis will show PaO_2 in mmHg. Each participant will contribute one value to each daily measure.

PANEL C Lowest daily PaO_2 by randomized allocation

Group means and standard errors will be shown at CRF day labels 0–7, with contributing participant counts. The x-axis will show CRF days and the y-axis will show PaO_2 in mmHg. Each participant will contribute one value to each daily measure.

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 recordings; panels B and C use the separately recorded daily Highest and Lowest fields. Group summaries weight participants equally. PaO2 collection is not restricted to ventilation. Observations end at recorded end of collection, death or first ICU discharge, as applicable. Day labels do not imply eight complete observation days. Later-day summaries condition on remaining observable; missing values are not filled. No repeated-measures treatment P value is planned.

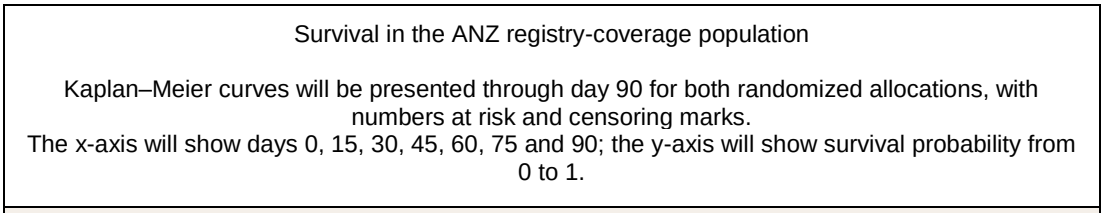


Figure S4. All-Cause Survival in the ANZ Registry-Coverage Population.
Deaths after index-hospital discharge will be included where registry coverage establishes follow-up. Follow-up will be censored at the last reliable all-cause observation or day 90. Reporting of this display is subject to the death registry linkage requirement in Section 27.