Mega ROX Brains
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 [1] and applies the statistical methods in the overarching Mega-ROX SAP, version 2.0 dated 9 November 2026 [2]. 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 liberal versus conservative oxygenation targets in adults with non-hypoxic ischemic acute brain injuries and conditions in the intensive care unit (Mega-ROX Brains).

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

2. Trial registration

Mega-ROX Brains is nested within the prospectively registered Mega-ROX trial (Australian New Zealand Clinical Trials Registry number ACTRN12620000391976). The registration identifies the parent research program; the Brains-specific hypothesis, population and analyses are specified in the Brains protocol and this detailed SAP.

3. SAP version

Version 2.0 dated 9 November 2026. This SAP was finalized blinded to study data prior to database lock. The online posting date is 10 November 2026, at https://www.doi.wellingtonicu.com/. Database-lock and results-access dates will be documented in the final report.

4. Protocol version

This SAP is based on the published Mega-ROX Brains protocol and statistical analysis plan [3] and the overarching Mega-ROX detailed SAP, version 2.0 dated 9 November 2026 [2].

The overarching SAP supplies the general statistical methods. Material amendments will be dated and their timing relative to access to results disclosed. This document specifies the analysis plan for the Brains population, liberal-versus-conservative contrast, diagnostic sensitivity analyses, four diagnosis subgroups and planned outputs. Necessary differences from the published Brains 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 Brains 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

Patients with acute brain injuries and conditions frequently require invasive mechanical ventilation for airway protection. Liberal oxygen therapy may improve the margin of safety against hypoxemia, including when cerebral oxygenation is impaired despite an apparently adequate systemic oxygen level. Hyperoxemia may also cause harm, and patients with preserved pulmonary gas exchange, including those without pulmonary pathology who are primarily intubated for airway protection, may be particularly susceptible to excessive oxygen exposure.

An exploratory ICU-ROX analysis suggested that the effect of oxygen therapy might differ between hypoxic ischemic encephalopathy (HIE) and other acute brain injuries and conditions [4]. Mega-ROX Brains was designed to provide a sufficiently large randomized comparison in the latter population. The published Brains protocol provides the detailed background and rationale [3].

8. Objectives

Research hypothesis: Among adults with acute brain injuries and conditions other than HIE who receive unplanned invasive mechanical ventilation in the ICU, liberal oxygen therapy, compared with conservative oxygen therapy, reduces in-hospital all-cause mortality up to 90 days after randomization.

Study objective: To estimate the effect of assignment to liberal rather than conservative oxygen therapy on the risk of in-hospital all-cause mortality during the index hospital admission up to day 90. Secondary objectives are to compare survival during that admission, live ICU and hospital discharge, recorded invasive ventilation duration, direct discharge home and ANZ registry-ascertained all-cause mortality by day 90.

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

Section 3 Trial Methods

9. Trial design

Mega-ROX Brains is an investigator-initiated, international, multicenter, individually randomized, parallel-group, two-sided superiority trial nested within the overarching Mega-ROX registry-embedded trial. Participants with a qualifying non-HIE acute brain injury or condition may also meet the criteria for the HIE or sepsis nested trials. These conditions are not treated as mutually exclusive.

The trial compares the assigned oxygen-management strategies. Treatment cessation, crossover, non-receipt and protocol deviations will be handled using a treatment-policy approach in the primary intention-to-treat analysis.

10. Randomization

Treatment was assigned using a secure, centralized, web-based interface with a computer-generated sequence. Clinical staff enrolled participants and communicated the allocation to the bedside team. No permuted block randomization or stratification was used. The sequence was concealed before allocation; the clinical intervention was open label.

The adaptive procedure could apply liberal-to-conservative allocation ratios of 1.05:1, 1:1.05 or 1:1. Four diagnostic groups informed allocation: suspected HIE after cardiac arrest, sepsis, non-HIE acute brain injury or condition, and none of these. When a participant fulfilled more than one diagnostic category, the overarching allocation hierarchy determined the applicable group; the hierarchy was based on the absolute mortality differences observed at the relevant interim analysis.

The probability actually applied to each participant, rather than an assumed probability based on the final diagnosis alone, will define the adaptive-randomization sensitivity weights. The schedule and hierarchy will be described in the Supplementary Methods, with reference to the overarching SAP and protocol [2,5].

11. Sample size

The Brains sample size is determined by the number of qualifying participants within the 40,003 unique participants in the completed overarching trial. The published Brains protocol initially anticipated approximately 9,000 participants. Based on the characteristics of the first 8,226 participants included in Mega-ROX, it anticipated approximately 8,000 Brains participants. Based on recruitment at the fourth interim analysis, the anticipated Brains sample size was 7,500. A range of potential sample sizes was considered in the published Brains protocol and statistical analysis plan.

Assuming mortality of 25% in the conservative-oxygen comparator group, 7,500 participants would provide 90% power to detect an absolute mortality reduction of 3.17 percentage points using a two-sided 5% significance level. This scenario is included in the published protocol power table. It describes the planning assumptions and is not a confirmed final Brains cohort count. Final enrollment, first allocations and data-use exclusions will be reported in the participant-flow diagram.

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.

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 [2,6].

13. Statistical interim analyses and stopping guidance

Overarching efficacy and safety analyses were planned after 1,000, 8,000, 16,000, 24,000 and 32,000 participants had been enrolled. The initial analysis primarily assessed recruitment and updated allocation ratios. At subsequent interim analyses, the overarching Haybittle–Peto symmetric stopping boundary was $P<0.001$, preserving the final two-sided alpha of 0.05. Mega-ROX was not stopped at an interim analysis.

For a diagnostic group, allocation remained 1:1 when the interim conservative-versus-liberal relative risk was between 0.9 and 1.1 and otherwise favored the lower-risk regimen by 1.05:1. The Brains protocol also describes a treatment-by-diagnostic-group interaction screen at $P<0.05$ before a Brains-specific efficacy assessment using $P<0.001$. The DMC record will distinguish the analyses actually undertaken from the planned overall and Brains-specific stopping procedures. No additional interim analyses are introduced by this SAP.

14. Timing of final analysis

Final analyses will use the completed follow-up and analysis population specified for the overarching trial. This SAP was finalized on 9 November 2026, blinded to study data and prior to database lock. Its online posting date is 9 November 2026. Database-lock and first treatment-results-access dates will be documented. Code will be developed using mock allocation labels where feasible.

The published Brains protocol specifies independent final analyses by two statisticians, with discrepancies resolved through consensus and discussion with the management committee when required. The actual analysis and review arrangements will be documented.

15. Timing of outcome assessments

Time zero for the 90-day outcome windows and event-time analyses is each participant’s randomization time. Primary mortality is assessed through day 90 during the index hospital admission. ICU and hospital discharge are followed through day 90, with death before live exit treated as the competing event. Supporting completed ICU and hospital episode durations will use all available follow-up to the recorded episode end or death, including beyond day 90. Post-discharge-inclusive day-90 mortality is restricted to the predefined ANZ registry-coverage population.

Oxygen exposure was recorded on CRF days 0–7 after randomization, subject to the collection limits in section 27. Total invasive ventilation hours are an aggregate for the index ICU episode and may include time before randomization; they do not have the same time origin as the event-time outcomes.

Section 4 Statistical Principles

16. Level of statistical significance

The primary treatment comparison will use a two-sided 5% significance level. The primary P value is the treatment test from the log-link risk-ratio model, including the stated convergence sequence if required. Supporting and exploratory analyses will be identified as such; their P values will not replace the primary test. Interpretation of the formal secondary comparisons will account for the Holm–Bonferroni procedure in Section 17.

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 (log-binomial treatment test). The log-binomial 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. Both raw and adjusted values will be reported in Table S11. 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. Failure of a supporting effect-estimation model will not replace an available pre-specified formal test.

Cox proportional hazards model effect estimates, supporting completed-duration analyses, sensitivity analyses, subgroup interactions and oxygen-exposure comparisons are outside the secondary Holm family. Ordinary 95% confidence intervals are pointwise and are not multiplicity-adjusted. Confirmatory conclusions for secondary outcomes will use their Holm-Bonferroni-adjusted P values.

18. Confidence intervals

Two-sided 95% confidence intervals will be reported for treatment effects. Confidence intervals for supporting and exploratory analyses will be interpreted in that context and will not be described as family-wise intervals.

19. Adherence and protocol deviations

The conservative regimen used the lowest FIO_2 consistent with SpO_2 at least 91%, with SpO_2 above 94% to be avoided and an upper alarm of 95% while supplemental oxygen was administered. The liberal regimen allowed clinician-directed oxygen with minimum FIO_2 0.30 during invasive mechanical ventilation. The default lower SpO_2 alarm of 90%, which clinicians could reduce as described in the protocol, is distinct from the protocol oxygen target.

The allocated regimen applied in ICU until discharge or day 90, whichever came first, and recommenced after ICU readmission during the index hospital admission. Temporary changes for transport or procedures were permitted. Other treatment was at clinical discretion. These permitted changes are not protocol deviations.

Deviations will be summarized by allocated group as participants affected and, where recorded, episodes and reasons. Categories can overlap. 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 definitions and analyses are specified in section 27.

20. Analysis populations and estimand

The primary Brains population comprises unique participants whose final baseline non-HIE acute brain injury or condition Y/N flag is Yes and whose study data may be used. The final flag may incorporate correction of an erroneous original response using the admission diagnosis or research-team clarification. HIE and sepsis may coexist with this flag. Final diagnostic categories define the primary adjustment and subgroup analyses; original classifications define only the specified diagnostic sensitivity analyses.

Within this cohort, analyses follow intention to treat using the first randomized allocation. Ineligibility, treatment cessation, crossover, protocol deviations and non-receipt do not exclude a participant from the primary intention-to-treat analysis. Withdrawal of treatment alone does not withdraw permission to use study data.

The primary estimand, summarized in the table below, is the relative risk, and corresponding absolute risk difference, of in-hospital all-cause mortality up to day 90 during the index hospital admission under assignment to liberal rather than conservative oxygen in the primary Brains population. Live discharge from the index hospital defines a non-event, including discharge not medically indicated under the treatment-policy strategy.

The primary analysis uses observed primary outcomes. Missing outcomes are addressed under section 31. The primary outcome will also be analyzed in eligible participants only and in eligible participants who purposefully received their assigned strategy. Analyses of these supporting populations do not replace the analysis of the intention-to-treat population.

Ventilation and direct-home outcomes use their respective collection populations, excluding site SA001 (KAIMARC). Post-discharge-inclusive all-cause mortality by day 90 uses the predefined ANZ registry-coverage population. Structural non-collection is distinct from missing information within a collecting population, and does not justify imputation across jurisdictions.

Objective: To determine whether liberal oxygen therapy, compared with conservative oxygen therapy, decreases the risk of in-hospital all-cause mortality up to 90 days after randomization in adults with non-HIE acute brain injuries and conditions.
Estimand: Relative risk, and corresponding absolute risk difference, of in-hospital all-cause mortality during the index hospital admission up to day 90 under assignment to liberal rather than conservative oxygen in the primary Brains population.
Treatment: Liberal oxygen therapy: Clinician-directed oxygen with a minimum FIO_2 of 0.30 during invasive mechanical ventilation in ICU. Conservative oxygen therapy: FIO_2 is reduced as rapidly as possible, to 0.21 where feasible, while maintaining SpO_2 at least 91%; SpO_2 above 94% is avoided and an upper alarm of 95% is used during supplemental oxygen. Full regimens and permitted changes are specified in the protocol and section 19.

ESTIMAND	ANALYSIS
Target population: Adults in ICU with a qualifying non-HIE acute brain injury or condition before randomization who receive unplanned invasive mechanical ventilation.	**Analysis set**: Unique randomized participants whose final baseline non-HIE acute brain injury or condition flag is Yes and whose study data may be used. Liberal oxygen is the treatment group and conservative oxygen the comparator. Only the first allocation is used after duplicate randomization. Final HIE and sepsis may coexist with the qualifying non-HIE brain condition.

Variable: In-hospital all-cause mortality during the index hospital admission on or before day 90 after randomization.	**Outcome measure**: Death during the index hospital admission by day 90. Live discharge or transfer out ends the index hospital episode and defines a non-event, as does verified survival in hospital at day 90. Later readmissions and deaths after index-hospital discharge do not change this outcome.
Handling of intercurrent events: Assigned treatment not received, treatment cessation, crossover and protocol deviations: Participants remain in their randomized groups using a treatment-policy strategy. Discharge when continued care remained medically indicated: Live index-hospital discharge defines a non-event using a treatment-policy strategy. Supporting hypothetical analyses are described alongside.	**Handling of missing data**: The primary analysis uses observed primary outcomes. Best–worst and worst–best scenarios are performed whenever outcomes are missing. Multiple imputation with 20 datasets will be used if either the best-worst or worst-best scenario changes the primary inference at the two-sided 5% level, as defined in section 31. Suitable overarching imputations will be reused if available; otherwise imputation will be performed within the final Brains Yes cohort only. **Supporting analyses**: 1. Eligible participants only. 2. Eligible participants who purposefully received their assigned regimen only. 3. Concordant-Yes cohort: Participants whose original non-HIE brain response at randomization and final baseline classification were both Yes, with permission to use data. 4. Original brain classification: All unique participants with an original non-HIE brain Yes response at randomization and permission to use data. 5. Expanded cohort: The final-Yes cohort plus original-Yes participants subsequently classified as No, with permission to use data. Hypothetical strategies for non-medically-indicated discharge: One analysis assigns affected liberal participants death and affected conservative participants survival; the other reverses these assignments. Verified deaths remain deaths. Recorded flags, including flagged participants with otherwise missing outcomes, determine these scenarios.
Population-level summary measure: Liberal-to-conservative relative risk and liberal-minus-conservative absolute risk difference in percentage points for in-hospital all-cause mortality up to day 90.	**Analysis approach**: A log-binomial model includes treatment allocation, final HIE and final sepsis indicators and a random site intercept. The constant non-HIE indicator is omitted in the primary cohort. A separate model with an identity link and the same covariates and site structure estimates the risk difference. The link-specific convergence sequences in section 27 apply.

Section 5 Trial Population

21. Screening data

Available screening data will be summarized in a CONSORT flow diagram. The figure will show how the Brains cohort was identified within Mega-ROX, numbers screened where available, reasons for exclusion or missed enrollment, allocated groups, data-use exclusions and numbers included in the primary analysis. Screening denominators unavailable for particular sites or periods will be identified.

Cross-classification of original randomization and final baseline Brains 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

Eligible patients are aged at least 18 years, have a qualifying non-HIE acute brain injury or condition before randomization, and receive unplanned invasive mechanical ventilation in the ICU. Enrollment is required within 12 hours of fulfilling eligibility criteria. Patients not enrolled within that window are described as missed, rather than excluded.

Qualifying diagnoses include traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, CNS infection and autoimmune CNS conditions. Cerebral venous sinus thrombosis and other qualifying CNS diagnoses will be displayed separately. Isolated seizures without a qualifying CNS condition, hepatic encephalopathy, delirium and neurological manifestations of non-CNS illness do not establish eligibility.

Previous enrollment and a clinician's judgment that participation is not in the patient's interests are exclusions. The latter includes circumstances in which either oxygen regimen is indicated or contraindicated, and imminent inevitable death. Eligibility deviations will be reported and will define the supporting eligible-only populations, without removing the participant from the primary intention-to-treat cohort.

23. Recruitment

Recruitment will be described by country and site, with the numbers assigned to each oxygen strategy. Participant flow will distinguish numbers randomized from unique participants and will show final diagnosis-based cohort selection, treatment receipt, withdrawal of data-use permission, primary-outcome availability and analysis denominators. The final Brains sample will be reported without replacing the historical sample-size assumptions.

24. Withdrawal and follow-up

Data will be retained and analyzed as permitted by the applicable consent and ethics arrangements. Withdrawal from assigned treatment or later follow-up will not remove earlier data unless permission for their use is also withdrawn. Losses to follow-up and reasons for unavailable outcomes will be summarized by allocation.

A known binary outcome remains usable when the exact event time is unavailable. An observed in-hospital death by day 90 establishes a primary event even if it cannot enter a timed analysis. A participant alive in hospital at day 90 is a primary non-event. Live index-hospital discharge establishes the primary non-event but does not alone establish all-cause day-90 survival.

25. Baseline descriptive measures

Baseline measures will be presented as means and standard deviations for approximately symmetric continuous variables, medians and quartiles for other continuous variables, and counts and percentages for categorical variables, with observed denominators. Treatment groups will not be compared using baseline significance tests. Clinically meaningful imbalances will be described.

The planned baseline table covers age, sex, body-mass index, clinical frailty, admission source, hospital- and ICU-admission-to-randomization times, diagnosis, coexisting HIE and sepsis, relevant

surgical classification and available oxygenation measures. The single admission diagnosis code defines mutually exclusive diagnosis categories. Final diagnostic flags define the principal summaries.

APACHE II will be reported descriptively where collected, and SAPS 3 will be reported descriptively for Brazil. APACHE II and SAPS 3 will not enter adjustment models because they may include measurements after randomization. Severity-score collection populations will be distinguished; the scores will not be treated as interchangeable.

Baseline PaO_2 and its paired FIO_2 refer to the pre-randomization measurement specified in the overarching SAP; later oxygen measurements do not replace baseline measurements. Where a paired value is unavailable, the PaO_2/FIO_2 ratio is missing.

When multiple imputation is required, baseline characteristics will also be described by primary-outcome availability. t tests or Wilcoxon rank-sum tests for continuous variables and chi-squared tests for categorical variables will inform the auxiliary predictors, together with clinical knowledge and the analysis covariates. Representativeness will compare ANZ Brains participants with adult ANZICS Adult Patient Database admissions with a recorded qualifying non-HIE brain condition and unplanned invasive ventilation at the same participating ICUs during their recruitment periods, using eligibility features observable in both sources. Similar comparisons of representativeness using data from other registries will be included where feasible. The comparison will be descriptive and will not use allocation-group baseline significance tests.

Section 6 Analysis

26. Outcome definitions

Outcome	Definition	Population	Principal estimate or test
Primary in-hospital mortality	Death during the index hospital admission on or before day 90 after randomization. Live discharge or transfer out, or verified survival in hospital at day 90, is a non-event.	Primary Brains cohort; observed primary outcomes.	Random-site-intercept log-binomial risk ratio; separate identity-link model for the risk difference. Both adjust for final HIE and sepsis.
Index-hospital survival	Time from randomization to in-hospital death. Follow-up ends at live discharge or transfer out, day 90 or the last reliable in-hospital observation. Post-discharge deaths do not enter this outcome.	Primary Brains cohort with usable timing.	Log-rank test. Supporting Cox hazard ratios are reported separately.
Live ICU discharge	Time from randomization to first live exit from the index ICU, including transfer to another ICU. Death before exit is a competing event. Follow to day 90; continuing admission is administratively censored.	Primary Brains cohort with usable timing.	Fine–Gray treatment test adjusted for final HIE and sepsis, with site-clustered robust standard errors.
Live hospital discharge	Time from randomization to live exit from the index hospital, including transfer out. Death before exit is a competing event. Follow to day 90; continuing admission is administratively censored.	Primary Brains cohort with usable timing.	Fine–Gray treatment test adjusted for final HIE and sepsis, with site-clustered robust standard errors.
Total invasive ventilation hours	Completed aggregate during the index ICU episode, potentially including pre-randomization hours and hours before death. This is a recorded resource-use duration, rather than time to live liberation.	Brains ventilation-collection population excluding SA001.	Quantile-regression treatment test adjusted for final HIE and sepsis, with site-clustered robust standard errors.
Direct discharge home	Live discharge directly from the index hospital to home by day 90. Death, transfer elsewhere and continuing admission are non-successes. An unknown destination after live discharge is missing.	Brains destination-collection population excluding SA001.	Random-site-intercept log-binomial risk-ratio treatment test adjusted for final HIE and sepsis; separate identity-link risk difference.
All-cause day-90 mortality	Death from any cause by day 90, including after hospital discharge. Reliable evidence of survival through day 90 establishes a non-event.	Predefined ANZ registry-coverage population within the primary Brains cohort.	Random-site-intercept log-binomial risk-ratio treatment test adjusted for final HIE and sepsis; separate identity-link risk difference.

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. Outcome-specific collection populations and observed analysis denominators will be reported

separately. Study-database ICU discharge dates are administrative for India, Malaysia, Nepal and Pakistan; registry dates will be checked for consistency where available, with study-database dates retaining precedence for analysis.

27. Analysis methods

Primary outcome and other binary outcomes: A binomial model with log link, treatment allocation, final HIE and final sepsis indicators and a random intercept for site will estimate the liberal-to-conservative risk ratio. A separate binomial model with identity link and the same covariates and site structure will estimate the risk difference. Events, observed denominators, proportions, risk ratios, risk differences and 95% confidence intervals will be reported.

Model convergence: The log-link and identity-link models will be assessed separately. If the initial model does not converge, the first successful model in the following sequence will be used: replace the random site intercept with site-clustered robust standard errors; combine sites with fewer than 10 participants and refit the original random-intercept model; combine sites with fewer than 20 participants and refit it; then refit the random-intercept model omitting HIE, omitting sepsis, and omitting both diagnostic terms. The link for the estimand is retained. The actual model used will be reported; an effect unavailable after this sequence will be reported as unavailable.

Survival: Kaplan–Meier curves will display survival during the index hospitalization, with numbers at risk and the two-sided log-rank test supplying the formal survival comparison. A Cox model with treatment alone and a second model with treatment, final HIE and final sepsis will provide supporting hazard ratios with site-clustered robust standard errors. The label will describe survival during the index hospitalization, rather than 90-day all-cause survival. The separate ANZ all-cause survival display is subject to the linkage requirement below.

The proportional hazards assumption will be assessed using Schoenfeld residuals. Departures will be reported without fitting an alternative model. If needed, sites with fewer than 10 and then fewer than 20 participants will be pooled according to the overarching procedure.

Live ICU and hospital discharge: Fine–Gray subdistribution-hazard models will include terms for treatment, final HIE and final sepsis, with site-clustered robust standard errors. Cumulative incidence functions for live discharge and competing death will be displayed. Subdistribution hazard ratios and 95% confidence intervals will be reported; a ratio above 1 indicates greater cumulative incidence of live discharge in the liberal group. For each outcome, the treatment test supplies its formal secondary P value in the Holm–Bonferroni family. The same small-site pooling sequence as applied to the index-hospital survival outcome will apply if needed. A cumulative-incidence median time to live discharge and its 95% confidence interval will be reported only if the cumulative incidence reaches 50%; otherwise the median will be reported as not reached.

Total ventilation hours: Quantile regression will include terms for treatment, final HIE and final sepsis and use site-clustered standard errors, using qreg2 in Stata or an equivalent implementation. The treatment coefficient is the conditional median difference in recorded total hours, liberal minus conservative, and its test supplies the formal ventilation P value in the Holm–Bonferroni family. Participants with zero recorded ventilation hours remain in this analysis and are counted separately. Pre-randomization ventilation time will not be subtracted.

Supporting duration comparisons: Quantile regressions of completed ICU and hospital durations, measured from randomization to the recorded episode end or death, will use all available follow-up, including beyond day 90, with the same covariates and site-clustered standard errors. Ongoing ICU or hospital episodes will be right-censored at the last available follow-up. Their censored elapsed times will not be treated as completed durations in quantile or log-linear models; their numbers and available follow-up will be reported separately by allocation. Positive completed total ventilation hours and completed ICU and hospital durations will also be compared using log-linear regressions, with exponentiated treatment coefficients reported as liberal-to-conservative geometric-mean ratios. Zero durations are excluded from log-linear models and their numbers reported. Medians, quartiles and geometric means will be shown by allocation and descriptively by survival to the end of the relevant

episode; ventilation uses ICU-episode survival. Survivor-restricted summaries condition on a post-randomization event.

Direct discharge home and all-cause day-90 mortality: The binary-model methods and separate link-specific fallback sequences apply within each pre-specified collection population. Site SA001 is excluded from destination and ventilation collection. The pre-specified formal all-cause day-90 mortality analysis is restricted to the ANZ registry-coverage population, and ANZ mortality reporting will distinguish registry-eligible participants from those with observed linked outcomes. No post-discharge mortality will be imputed in jurisdictions where it was not collected. Day-90 all-cause mortality, including deaths after hospital discharge, will be reported in the primary manuscript only if death registry linkage to the ANZICS Adult Patient Database (APD) covers dates beyond the final Mega-ROX trial participant's day-90 follow-up. Otherwise, reporting of this outcome will be deferred.

Table S11 identifies the formal comparisons in the applicable family and gives available raw and Holm–Bonferroni-adjusted P values. Supporting Cox, quantile and geometric-mean estimates will not replace these tests. Oxygen-exposure methods are specified below.

Oxygen fields and observation window: Website CRFs at all sites record days 0–7, with PaO_2 and FIO_2 scheduled at 06:00, 12:00, 18:00 and 24:00 and separate daily Lowest and Highest fields. Scheduled and extreme FIO_2 values apply while ventilated; the PaO_2 block has no corresponding ventilation restriction. Observations end at the recorded end of collection, death or first ICU discharge, whichever occurs first. The eight labels on the CRF do not imply eight complete days or a common 168-hour denominator.

Duration blocks separately record hours with SpO_2 ≥97%, hours with SpO_2 <88%, Total SpO_2 Hours, hours with FIO_2 0.21 and Total FIO_2 hours. The room-air block covers ventilation and the period after extubation. For each participant and metric, threshold hours and the corresponding total are summed over days on which both are recorded; percentage exposure is 100 times the ratio of those sums. Daily percentages are not averaged. A missing numerator is not zero and removes that day from both sums. A zero summed denominator supplies no percentage; zero threshold hours with a positive total are included.

At least one PaO_2 >100 mmHg will be identified using the separate daily Highest fields, and at least one PaO_2 <60 mmHg using the separate daily Lowest fields. Each denominator comprises participants with at least one corresponding recorded extreme. The denominator and missingness will be reported separately for each measure.

Percentages and recorded exposure hours will be compared by quantile regression with site-clustered robust standard errors. PaO_2 threshold proportions will use log-binomial models with a random site intercept and the applicable convergence sequence. Exposure differences are liberal minus conservative and ratios liberal/conservative. These tests are outside the secondary Holm family.

For daily displays, each participant's daily mean is calculated from available scheduled readings, without filling missing times; separate fields provide daily minima and maxima. Group means and standard errors will weight contributing participants equally and show participant counts by allocation, measure and day. PaO_2 will be reported in mmHg and FIO_2 as a fraction. No values will be imputed after death or first ICU discharge; ventilation additionally limits the ventilated-FIO_2 fields. Later days condition on remaining observable. Achieved oxygen exposure is not itself randomized.

28. Adjustment for covariates

The principal models will include terms for final HIE and sepsis indicators and adjust standard errors for site. An additional primary-outcome model will include terms for age and sex, followed by a model also including baseline characteristics with clinically meaningful imbalances between allocations within the primary Brains population. Covariates included because of clinically meaningful imbalances will be selected from summaries with treatment allocation masked, before treatment-effect results are examined. The selected covariates, their clinical rationale and the order in which they are considered will be documented in the analysis record before fitting the additional model. Selection will not be based on baseline P values or treatment findings. APACHE II and SAPS 3 are excluded.

If additional-adjustment models fail, the overarching convergence procedures apply. Additional covariates will be omitted one at a time in the order imbalanced baseline variables, age, then sex; if necessary, pairs will be omitted in the corresponding order specified in the overarching SAP. Treatment remains in the model. The covariates and denominators will be reported.

29. Sensitivity analyses

Eligibility and receipt: The primary analysis will be repeated in eligible participants only and in eligible participants who purposefully received their assigned regimen. Eligibility and receipt are classified independently. These supporting analyses use the primary endpoint, effect direction, diagnostic adjustment, site model and convergence sequence.

Concordant brain classification: The primary-outcome analysis will be repeated in unique participants whose original non-HIE brain response at randomization and final baseline classification were both Yes, with permission to use data. This concordant-Yes cohort excludes participants whose original No response was corrected to Yes.

Original brain classification: The primary-outcome analysis will be repeated in all unique parent-trial participants with an original non-HIE brain Y/N response of Yes at randomization and permission to use data. This cohort will include original Yes records corrected to No and exclude original No records corrected to Yes.

Effect of corrections: The primary-outcome analysis will be repeated in the expanded population comprising the final-Yes cohort together with participants whose original non-HIE brain response was Yes and final classification was No. Original No-to-Yes participants will remain included. This estimate will be presented alongside the primary final-Yes, concordant-Yes and original-Yes estimates to assess the effects of additions and removals.

Discharge when continued care was medically indicated: The contemporaneous ICU-to-home discharge flag will define two hypothetical analyses. In one, affected participants are assigned death under liberal allocation and survival under conservative allocation; in the other, assignments are reversed. Verified deaths remain deaths. Flagged participants with otherwise missing primary status receive the scenario assignment. The flag will not be inferred from country or destination alone.

To assess the sensitivity of the primary outcome conclusions to potential bias induced by response-adaptive randomization, the primary analyses of the primary outcome (i.e. estimation of the risk ratio and risk difference) will be repeated using inverse probability of treatment weights, with each participant weighted by the reciprocal of the probability of receiving the treatment actually assigned. Categorical randomization epoch will be included to account for temporal population drift. Epochs will be defined by the dates on which updated randomization probabilities were implemented. The probability and hierarchy actually applied at allocation will be used. Risk ratios and differences retain their respective link functions, and the applied allocation schedule and weight range will be reported.

All diagnostic sensitivity analyses retain first allocation, liberal-versus-conservative orientation, final HIE and sepsis adjustment and the primary site and convergence methods. Cohort counts, events, sites and overlap with the primary population will be reported by allocation, with risk ratios, risk differences and confidence intervals. Diagnostic sensitivities are supporting analyses outside the secondary Holm-Bonferroni family. Missing-primary-outcome sensitivities are described in section 31.

30. Subgroup analyses

The four protocol-defined subgroup pairs for the primary outcome are traumatic brain injury versus no traumatic brain injury; subarachnoid hemorrhage versus no subarachnoid hemorrhage; intracerebral hemorrhage or ischemic stroke versus neither; and CNS infection versus no CNS infection. These analyses will be performed regardless of the overall primary result. The principal analysis uses final admission diagnosis codes.

For each pair, the primary model will include treatment, the subgroup main effect, the treatment-by-subgroup interaction, final HIE and sepsis indicators and the random site intercept. An existing main effect will not be duplicated. Subgroup-specific effects and interaction P values will be reported; each binary interaction has one degree of freedom where estimable.

These exploratory interactions are outside the secondary Holm–Bonferroni family. Sparse interactions that cannot be estimated will be reported as unavailable.

31. Missing data

Outcome availability and reasons for missingness will be reported by allocation and endpoint. Structural non-collection, unresolved outcomes within collecting populations and unavailable exact timing will be distinguished. Known binary outcomes will be retained when times are missing. Death or live discharge ends relevant event-time follow-up and is not itself missing follow-up.

The primary analysis will use participants with observed primary outcomes. Whenever any primary outcomes are missing, worst–best and best–worst scenarios will assign all missing outcomes in one allocation to death and those in the other to non-death, then reverse the assignments. A primary non-event includes survival in hospital at day 90 as well as prior live discharge.

If either extreme scenario changes the conclusion at the two-sided 5% level, multiple imputation with 20 datasets will also be performed as specified below. A change means that the primary treatment test moves between $P<0.05$ and $P\geq0.05$ or that a statistically significant finding favors the opposite treatment. Complete-case and imputed results will both be reported when imputation is required. If primary outcomes are complete in the final Brains Yes cohort, no primary-outcome imputation or extreme-scenario analysis is required for the primary analysis.

When multiple imputation is required for the Brains analysis, the 20 imputed datasets generated for the overarching Mega-ROX analysis will be reused if available and suitable for the applicable participants and outcome, retaining the relevant Brains analysis and outcome-specific collection populations. If suitable overarching imputations are unavailable, including when the overarching analysis does not require imputation, 20 datasets will be generated within the final Brains Yes cohort only, intersected with the outcome-specific collection population. First allocation and permission to use data apply.

For this Brains-specific imputation, outcomes will be imputed separately by allocated group using analysis covariates and relevant baseline predictors of outcome or missingness. 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. Auxiliary predictors will be informed by clinical knowledge, analysis covariates and the baseline comparisons by primary-outcome availability described in section 25. 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. No extubation or liberation time or structurally uncollected outcome will be imputed.

Under this fallback, primary in-hospital mortality will be imputed within the final Brains analysis population when indicated. When required, ANZ all-cause day-90 mortality will be imputed separately using logistic regression within the final Brains Yes cohort intersected with its intended ANZ registry-coverage population. Structural non-collection will not be imputed. Imputed distributions will be compared with observed data using density plots for continuous outcomes and proportion plots for binary outcomes.

If a selected model fails in more than one quarter of imputed datasets, the pre-specified convergence sequence will be followed. A method succeeds when it converges in at least 75% of datasets; the number fitted and any omissions will be reported. 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, when required, will reuse suitable overarching datasets if available; otherwise it will use the Brains-specific procedures and populations above. Censored live-discharge times will not be treated as completed durations for ordinary chained-equation imputation; the planned event-time analyses will use the available event and follow-up information.

32. Harms

Adverse events were not systematically ascertained. Expected abnormalities and complications of critical illness were not routinely reportable serious adverse events; sites reported events potentially related to the intervention or otherwise of concern, as in the overarching reporting arrangements [2,7].

Table S10 will summarize all adverse-event reports recorded for the primary Brains 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. Safety comparisons will be descriptive. These summaries describe reported events, rather than systematic ascertainment of every complication; 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. Exact versions and packages will be recorded. The specified qreg2 approach will be used for quantile regression with site-clustered standard errors.

The general model syntax and implementation are described in the overarching SAP; Brains models omit the constant non-HIE indicator, retain final HIE and sepsis, and code treatment effects as liberal relative to conservative. The actual model and convergence fallback used for each estimate will be reported. Independent statistical review will follow section 14.

Illustrative specifications use a treatment indicator coded 0 for conservative oxygen and 1 for liberal oxygen. Variable names below are illustrative; HIE and sepsis denote final diagnostic indicators. Event and follow-up definitions follow section 26.

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

Final variable names, treatment coding and syntax will be checked. Primary results, counts and Holm–Bonferroni calculations will be independently verified against the approved plan. Material deviations will be documented.

34. Modifications from the published SAP

Primary population and diagnostic sensitivity analyses: The primary cohort will use final corrected baseline Brains status, with concordant-Yes, original-status and expanded-cohort sensitivity analyses. Final HIE and sepsis categories will determine principal-model adjustment. Original and final classifications will remain distinct in diagnostic sensitivity analyses [8].

Site modeling: The published Brains SAP places site adjustment in sensitivity analyses. The primary binary models now include a random site intercept, matching the overarching SAP and supplied manuscript methods [2,9]. Separate identity-link risk differences, log-link risk ratios and the original convergence sequence are retained.

Additional covariates: The published plan includes age, sex and illness severity [3]. The overarching approach retains age and sex and clinically meaningful baseline imbalances, with APACHE II and SAPS 3 excluded because these scores may not be pre-randomization measurements.

Ventilation: The published plan and template propose time to live liberation with a competing-risk analysis [3,9]. The collected measure is total invasive ventilation hours in the index ICU episode, including possible pre-randomization time. The formal comparison therefore uses adjusted quantile regression of recorded totals.

Other secondary outcomes: Live ICU and hospital discharge retain Fine–Gray analysis. Supporting quantile and positive-duration log-linear comparisons follow the overarching SAP. Completed ICU and hospital durations will use all available index-episode follow-up, including beyond day 90, whereas the formal live-discharge event-time analyses retain their 90-day horizon. Ongoing episodes at last follow-up will be reported as censored rather than as completed durations. All-site survival is restricted to the index hospitalization, whereas all-cause day-90 mortality uses ANZ registry coverage. The formal comparisons follow the published Brains plan [3,9]. Section 17 specifies their Holm adjustment and the conditional inclusion of ANZ mortality.

Power and subgroup definitions: The anticipated sample of 7,500 with a 25% conservative-group mortality risk and a 3.17 percentage-point detectable difference is retained as a historical planning scenario. The four published binary diagnosis pairs, including traumatic brain injury and the combined stroke category, are retained. The planned outputs will use the index-hospital day-90 endpoint and the corresponding survival, discharge and duration definitions.

Alignment with the overarching SAP version 2.0 dated 9 November 2026 [2] includes data-source selection, allocation-masked selection of additional covariates, implementation-date randomization epochs, and conditional outcome-specific imputation. This revision adds the estimand and outcome summary tables and illustrative model code, reuses suitable overarching imputed datasets when available with a fallback within the final Brains Yes cohort only, and clarifies cohort-specific additional adjustment and descriptive safety reporting. Comparisons in the applicable Holm family without a valid P value will remain in that family, with P=1 used solely for adjustment. Approval, public-posting, database-lock and results-access dates, actual cohort counts, allocation records and analysis denominators will be reported with the final analyses.

35. References

1. Conservative Oxygen for ICU Patients with Post-Cardiac-Arrest Brain Injury: the LOGICAL trial. Detailed statistical analysis plan. Final version 1.0, 14 November 2025. Reference for structure and level of detail.

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

3. Young PJ, et al. Protocol and statistical analysis plan for the mega randomised registry trial comparing conservative vs. liberal oxygenation targets in adults with nonhypoxic ischaemic acute brain injuries and conditions in the intensive care unit (Mega-ROX Brains). Critical Care and Resuscitation. 2023;25:53–59. doi:10.1016/j.ccrj.2023.04.011.

4. Young PJ, Mackle D, Hodgson C, et al. Conservative or liberal oxygen therapy for mechanically ventilated adults with acute brain pathologies: A post-hoc subgroup analysis. Journal of Critical Care. 2022;71:154079. doi:10.1016/j.jcrc.2022.154079.

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

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

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

8. Mega-ROX Brains detailed statistical analysis plan. Version 0.3, 25 October 2026. Source of the prior diagnostic sensitivity analyses.

9. Liberal Oxygen for Mechanically Ventilated ICU Patients with Brain Injuries. Manuscript template, including mock tables and figures.

36. Appendix planned tables and figures

The tables and figures present the planned analyses with outcome-specific populations and denominators. Ratios compare liberal with conservative oxygen; differences are liberal minus conservative.

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
Diagnosis – no. (%)		
Traumatic brain injury	xxx (xx.x)	xxx (xx.x)
Subarachnoid hemorrhage	xxx (xx.x)	xxx (xx.x)
Intracerebral hemorrhage	xxx (xx.x)	xxx (xx.x)
Ischemic stroke	xxx (xx.x)	xxx (xx.x)
Central nervous system infection	xxx (xx.x)	xxx (xx.x)
Cerebral venous sinus thrombosis	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)
Coexisting HIE – no. (%)	xxx (xx.x)	xxx (xx.x)
Coexisting sepsis – no. (%)	xxx (xx.x)	xxx (xx.x)
Surgical/medical classification – no. (%)		
Surgical	xxx (xx.x)	xxx (xx.x)
Non-surgical/medical	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. Surgical/medical classification uses study-database ICNARC coding and is separate from physical ICU admission source; it does not distinguish elective from emergency surgery.

† 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. APACHE II will be reported descriptively where collected.

¶ 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: 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)	[median (IQR)]	[median (IQR)]	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=XXXX)**	**Conservative oxygen (n=XXXX)**	**Estimate (95% CI)**
Primary outcome			
Mortality in the index hospitalization within 90 days, n (%)	xxxx (x.xx)	xxxx (x.xx)	Relative risk x.xx (x.xx to x.xx)† Risk difference x.xx (x.xx to x.xx)
Secondary outcomes			
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 until discharged alive from ICU			
Number of patients	xxxx	xxxx	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subdistribution HR [95% CI]‡
Days until discharged alive from hospital			
Number of patients	xxxx	xxxx	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subdistribution HR [95% CI]‡
Discharged directly home from hospital, n (%)	xxxx (xx.x)	xxxx (xx.x)	Relative risk§ x.xx (x.xx to x.xx) Risk difference x.xx (x.xx to x.xx)
Survival during the index hospitalization, deaths/N	[deaths/N]	[deaths/N]	Cox HR [95% CI]¶

* Primary P=[P] is from the risk-ratio model. All 95% confidence intervals are pointwise. Table S11 gives the secondary raw and Holm-adjusted P values. Table S7 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 sepsis indicators and a random site intercept, following the overarching convergence sequence. 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 and hospital exit will adjust for the same diagnoses with site-clustered errors and death competing. A cumulative-incidence median will be reported only if live discharge reaches 50%. § Direct-home analyses will exclude SA001; 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.

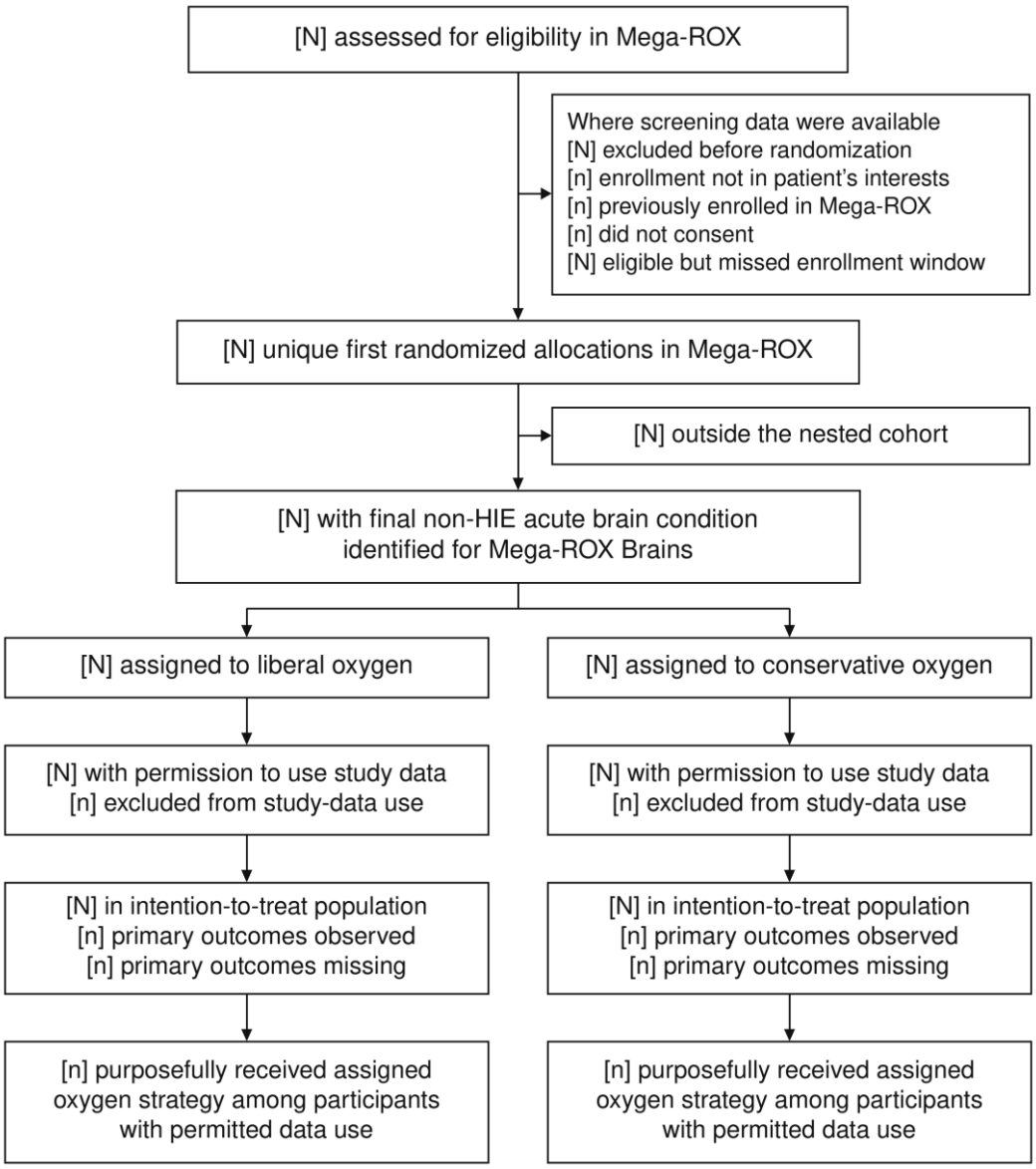


Figure 1. Randomization and Follow-up.
Screening in Mega-ROX, identification of the final diagnostic cohort, first allocations, data-use exclusions, and primary-outcome availability. Purposeful receipt of the assigned strategy is reported among participants with permitted data use. Participants outside the nested cohort are not exclusions from the overarching trial. All counts are placeholders.

Mega-ROX Brains 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 mortality risk ratios for traumatic brain injury versus no traumatic brain injury; subarachnoid hemorrhage versus no subarachnoid hemorrhage; intracerebral hemorrhage or ischemic stroke versus neither; and CNS infection versus no CNS infection. Risk ratios will be presented with 95% confidence intervals, events and denominators. Each one-degree-of-freedom interaction P value will be shown; 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 sepsis 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. Ventilation and direct-home analyses exclude SA001 (KAIMARC); SA002 (KFSHRC) is included. Structural non-collection will not be imputed.

† ICU admission source is categorized as emergency department, operating theater/recovery, ward, another hospital (not ICU), or another ICU. ‡ Study-database ICNARC coding classifies patients as surgical or non-surgical/medical only. It does not distinguish elective from emergency surgery or identify physical ICU admission source; source-of-admission fields are listed separately above.

¶ Hospital discharge destination is categorized as died, home, another medical care facility, or another destination. ¥ Day-90 all-cause mortality includes deaths after hospital discharge. Registry sources are recorded for ANZ, India, Malaysia, Nepal and Pakistan. The pre-specified formal day-90 mortality comparison remains restricted to the ANZ registry analysis population.

Collection notes: CA001 used REDCap for its first 34 participants. SA002 used REDCap, without the Mega-ROX hospital-discharge form. Brazil could record hospital outcomes in both databases. Study-database ICU discharge dates are administrative for India, Malaysia, Nepal and Pakistan. Registry dates will be checked for consistency where available; study-database dates retain precedence for analysis.

Abbreviations: ANZ, Australia/New Zealand; SA001 and SA002, Saudi Arabian study-site identifiers; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRF, case report form, including REDCap; ICU, intensive care unit; N/A, not available; R, registry; SD, study database. Brazil collected SAPS 3 only. Source designations do not establish completeness or successful linkage.

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

Allocation epoch (start date)	Brains 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: [ratio] Other brain condition: 1.05:1 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 Brains cohort. Each participant's actual allocation probability, accounting for overlapping diagnoses and the hierarchy applied at randomization, will be used for weighting. The Brains cohort includes participants whose allocation probability was governed by another diagnostic group. Ratios in this table are liberal to conservative; the initial non-HIE brain-condition 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: 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 Brains participants and adult ANZICS Adult Patient Database admissions with a recorded qualifying non-HIE brain condition and unplanned invasive ventilation at participating ICUs during the same recruitment periods. Eligibility matching and characteristics will be restricted to features observable and defined comparably 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 S5: 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: F_IO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, arterial partial pressure of oxygen; SaO_2, arterial oxygen saturation; SpO_2, oxygen saturation measured by peripheral pulse oximetry.

Table S6: Additional Analyses of Primary and Secondary Outcomes*

	Liberal oxygen (n=XXX)	Conservative oxygen (n=XXX)	Difference or 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 received allocated treatment	[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 with 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]
Concordant-Yes: original non-HIE brain Yes and final Brains Yes	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Original randomization non-HIE brain-condition Yes population	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Final Brains Yes cohort plus original-Yes/final-No participants	[n/N (%)]	[n/N (%)]	[RD; 95% CI]	[RR; 95% CI]
Secondary completed-duration analyses				
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	
Completed ICU duration, days: conditional median difference	[median (IQR)]	[median (IQR)]	[median difference; 95% CI]	
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	
Completed hospital duration, days: conditional median difference	[median (IQR)]	[median (IQR)]	[median difference; 95% CI]	
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 sepsis indicators. The model, population and denominator will be reported for each analysis. Twenty primary-outcome imputations will be used if either extreme missing-outcome scenario changes the primary 5% inference or reverses a statistically significant direction. Suitable overarching datasets will be reused if available; otherwise imputation will be performed within the final Brains Yes cohort only. Diagnostic sensitivities will follow section 29; original and final classifications will remain distinct.

† Completed ICU and hospital durations will also be compared using quantile regression; the adjusted conditional median differences will be liberal minus conservative and reported 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 and 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 S8). 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 S7: 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 (%)]
Observed day-90 vital status	[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 S8: 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. Known binary outcomes will be retained when exact event times are 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 S9: 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 Brains cohort. The concordant-Yes sensitivity includes only participants with original Yes and final Yes classifications. Each nested analysis will retain its own denominator. Multiple qualifying conditions may coexist, whereas the single admission diagnosis code defines mutually exclusive descriptive categories. Cohort counts and primary-outcome sensitivity estimates will be presented in Table S6.

Table S10: 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 S11: 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. Failure of a supporting effect-estimation model will not replace an available pre-specified formal 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

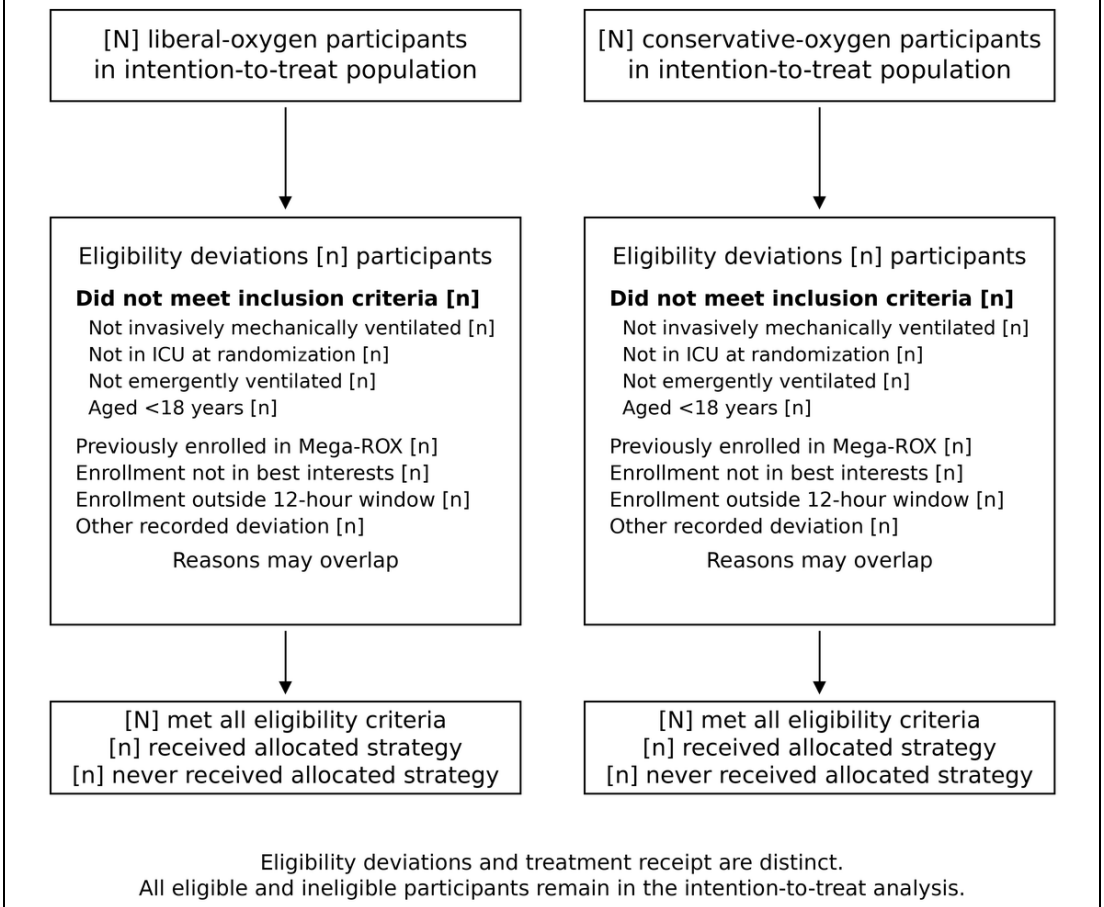


Figure S1. Protocol Deviations Affecting Trial Eligibility.
Participants and recorded reasons are summarized by randomized allocation. Reasons may overlap. Failure to receive treatment is classified separately from eligibility.

Mega-ROX Brains 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. FIO_2 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. PaO_2 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.

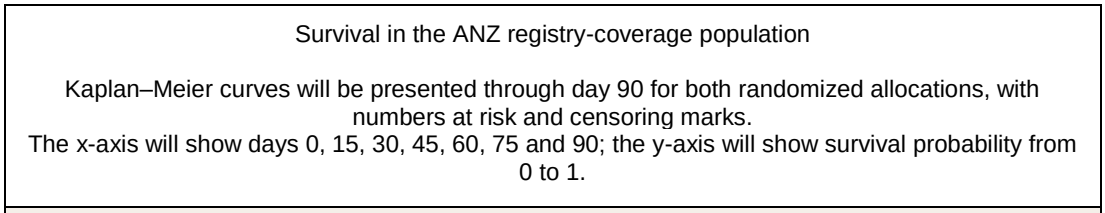


Figure S4. All-Cause Survival in the ANZ Registry-Coverage Population.
Deaths after index-hospital discharge will be included where registry coverage establishes follow-up. Follow-up will be censored at the last reliable all-cause observation or day 90. Reporting of this display is subject to the death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