Mega ROX HIE
Detailed Statistical Analysis Plan

Version 2.0 | 9 November 2026

Finalized blinded to study data prior to database lock.

Online posting date: 10 November 2026

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

This plan specifies the population, outcomes and analyses for Mega-ROX HIE. It follows the structure of the final LOGICAL SAP [1] and applies the general statistical methods in the overarching Mega-ROX SAP version 2.0 dated 9 November 2026 [2]. The HIE population, hypothesis and pre-specified subgroup are retained. The appendices contain the planned tables and figures.

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Section 1 Administrative Information

1. Title

Mega randomized registry trial comparing conservative versus liberal oxygenation targets in adults in the intensive care unit with suspected hypoxic ischemic encephalopathy following a cardiac arrest (Mega-ROX HIE).

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

2. Trial registration

The Mega-ROX trial program was prospectively registered with the Australian and New Zealand Clinical Trials Registry as ACTRN12620000391976. Mega-ROX HIE is a pre-specified nested trial within that program. The registration identifies the parent research program; the HIE-specific hypothesis, population and analyses are specified in the HIE 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, with posting at https://www.doi.wellingtonicu.com/. Database-lock and results-access dates will be documented in the final report.

4. Protocol version

This document is based on Young PJ et al. Protocol and statistical analysis plan for the mega randomised registry trial comparing conservative vs. liberal oxygenation targets in adults in the intensive care unit with suspected hypoxic ischaemic encephalopathy following a cardiac arrest (Mega-ROX HIE). Critical Care and Resuscitation. 2024;26:87–94. doi:10.1016/j.ccrj.2024.03.004 [3].

Shared intervention and registry pathways follow the overarching Mega-ROX protocol [4]. General statistical methods follow the overarching detailed Mega-ROX SAP version 2.0 dated 9 November 2026 [2]. Material amendments will be dated and their timing relative to access to results disclosed.

This document specifies the analysis plan for the HIE population, conservative-versus-liberal contrast, diagnostic sensitivity analyses, the subgroup analysis and planned outputs. Necessary differences from the published HIE 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 HIE 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 who remain unconscious after resuscitation from cardiac arrest may have hypoxic ischemic encephalopathy (HIE). The published protocol describes the rationale for reducing exposure to supplemental oxygen to limit reperfusion injury and the uncertainty about whether conservative oxygen therapy improves survival. Mega-ROX HIE tests this question among adults receiving invasive mechanical ventilation in ICU.

Mega-ROX HIE is one of three nested trials within the international Mega-ROX program. Participants may also meet the definitions for Mega-ROX Sepsis or Mega-ROX Brains. These overlaps are retained and represented by separate final sepsis and non-HIE brain-condition indicators in the pre-specified adjustment models. LOGICAL is a further nested study within a subset of Mega-ROX HIE sites and participants. Participation in LOGICAL is not an exclusion from Mega-ROX HIE.

The HIE study concerns the in-hospital and other outcomes collected across its participating jurisdictions. LOGICAL provides separate long-term neurological and functional follow-up in its own population; these outcomes were not collected for the full Mega-ROX HIE cohort. The findings of the LOGICAL trial have been published previously [5].

8. Objectives

Research hypothesis: Among adult ICU patients with suspected HIE following a cardiac arrest who receive invasive mechanical ventilation, conservative oxygen therapy, compared with liberal oxygen therapy, reduces in-hospital all-cause mortality during the index hospital admission within 90 days after randomization.

The primary objective is to estimate the effect of assignment to conservative rather than liberal oxygen therapy on this mortality risk. Secondary objectives are to compare index-hospital survival, live ICU discharge, live hospital discharge, recorded total invasive ventilation hours, direct discharge home and all-cause mortality by day 90 in the population with post-discharge registry coverage.

Oxygen exposure, delivery of the allocated strategy and reported adverse events will be described. The subgroup analysis specified in the HIE protocol examines whether the primary treatment effect differs between patients admitted to ICU from the emergency department and those admitted from elsewhere.

Section 3 Trial Methods

9. Trial design

Mega-ROX HIE is an investigator-initiated, international, multicenter, individually randomized, parallel-group, two-sided superiority trial embedded in the overarching registry-based Mega-ROX program. Conservative oxygen therapy is the intervention and liberal oxygen therapy the comparator for this HIE analysis.

The index ICU and hospital admissions are the episodes during which randomization occurred. Randomization is time zero for the 90-day outcome windows and event-time analyses. Completed total ventilation hours are an exception to a strictly post-randomization duration because only the total for the index ICU episode was collected.

The study is open label for patients and treating teams. The published protocol describes blinded statistical work using mock treatment codes and independent final analyses by two statisticians. The final report will state the procedures actually used and the timing of SAP approval relative to access to actual treatment assignments.

10. Randomization

Treatment assignment was performed using a secure, centralized, web-based system. The permitted randomization ratios were 1.05:1 favoring liberal oxygen, 1:1.05 favoring conservative oxygen, and 1:1. Randomization probabilities could change after interim analyses, using the mortality experience in the governing diagnostic groups in the overarching trial.

The governing groups were HIE, sepsis, other acute brain injury or condition, and none of these conditions. For patients meeting more than one group, the hierarchy used to determine allocation probabilities followed the overarching protocol. This governing group is distinct from all diagnostic indicators retained in the final analysis. Computer-generated sequences were concealed; no stratification or permuted blocks were used.

The initial and subsequent probabilities, implementation-date epochs and hierarchy applying to HIE participants will be reported in Table 8. Epochs are defined by the dates on which updated randomization probabilities were implemented. The probability actually applied to each participant, including participants with corrected diagnostic classifications, will be used in inverse-probability weighting and will not be reconstructed from final diagnosis.

11. Sample size

The nested HIE sample size was determined by the proportion of the planned 40,000 overarching participants with suspected HIE. The published Mega-ROX HIE protocol describes an original expectation of approximately 6,880 HIE participants [3] based on the 17.2% proportion in ICU-ROX [6]. With a liberal-group mortality risk of 54.4%, this was expected to give more than 90% power to detect a 4 percentage-point absolute difference at a two-sided 5% significance level [3].

When the HIE protocol was published, 1,261 of the first 12,529 Mega-ROX participants (10.1%) met the HIE criteria, suggesting a final HIE sample of approximately 4,000 [3]. The published scenario table shows that, with 4,000 participants, a 50% control event rate and no loss to follow-up, a 5.12 percentage-point absolute difference is detectable with 90% power and two-sided alpha 0.05 [3]. The ANZCTR registration subsequently confirmed an anticipated HIE sample of approximately 4,000, based on the proportion enrolled with HIE at the fourth interim analysis [7]. These are planning assumptions, not observed final event rates or a new sample-size calculation.

The retained overarching trial cohort comprises 40,003 unique participants. The final HIE count, consent exclusions and primary-outcome denominator will be reported separately. The published sample-size figures are planning assumptions; achieved enrollment and estimate precision will be reported without retrospective observed-power calculations.

12. Framework

The primary comparison uses a superiority framework with two-sided testing. Conservative oxygen is the intervention and liberal oxygen is the comparator. Risk ratios and geometric-mean ratios compare conservative with liberal oxygen. Risk differences and median differences are conservative minus liberal. Risk differences will be expressed in percentage points. All treatment effect estimates will be reported with 95% confidence intervals.

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

13. Statistical interim analyses and stopping guidance

The overarching trial conducted interim reviews after 1,000, 8,000, 16,000, 24,000 and 32,000 participants had been enrolled. The initial review primarily assessed recruitment and updated randomization probabilities. Subsequent efficacy reviews used a symmetric Haybittle–Peto boundary of $P<0.001$. Mega-ROX did not stop at an interim analysis.

The published HIE protocol specifies an HIE-specific interim efficacy analysis only when there was evidence of treatment-effect heterogeneity between participants with and without HIE (interaction $P<0.05$), with an HIE stopping boundary of $P<0.001$ if that analysis was undertaken. The final report will describe the HIE reviews actually triggered and undertaken; this SAP does not retrospectively change the interim rules.

The independent data monitoring committee and the processes for adaptive allocation and recommendations to the management committee are described in the published protocol and overarching SAP. No additional final-analysis alpha adjustment beyond the pre-specified approach is introduced here.

14. Timing of final analysis

The final analysis will use the completed 90-day follow-up for the HIE participants in the completed overarching trial. The final approved SAP, public-posting details, database-lock date and timing of access to actual treatment results will be documented. Analysis code will be developed using dummy treatment labels where feasible.

The published HIE plan envisaged independent analyses by two statisticians with discrepancies resolved by discussion and, if necessary, the management committee. The analysis report will identify the statisticians and document material departures from the approved plan.

15. Timing of outcome assessments

The primary outcome is assessed through 90 days after randomization during the index hospital admission. Index-hospital survival and time to live ICU or hospital discharge are followed to day 90 or the earlier end of relevant observation. Direct discharge home is assessed from the index-hospital outcome and destination by day 90. Supporting completed ICU and hospital episode durations will use all available follow-up to the recorded episode end or death, including beyond day 90.

All-cause mortality by day 90 uses the predefined Australia and New Zealand (ANZ) registry-coverage population, including ascertainment after index-hospital discharge. Oxygen measurements use the website case-report-form (CRF) columns labeled day 0 through day 7, ending at the recorded end of collection, death or first ICU discharge, whichever occurs first. These labels do not imply eight complete days or 168 hours of observed exposure.

No day-180 GOS-E, quality-of-life, cognition or neurological-function assessment is specified for the full HIE trial. Such assessments were already reported for LOGICAL and will not be added as HIE outcomes.

Section 4 Statistical Principles

16. Level of statistical significance

The primary treatment test is two sided at the 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. Unless stated otherwise, other tests are also two sided. 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. Raw and adjusted P values will both be shown. The primary outcome is tested separately and is not part of the secondary family.

Additional covariate models, geometric-mean and completed-duration summaries, oxygen-exposure analyses, sensitivity analyses and interaction tests are supporting or exploratory, and their 95% confidence intervals will not be adjusted for multiplicity. 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 tests will not add to or replace the formal comparisons.

18. Confidence intervals

Confidence intervals will be two-sided 95% intervals. Secondary-outcome tables will explicitly state that these intervals are pointwise and not adjusted for multiplicity. Risk differences will be presented in percentage points; median differences in their recorded units; and relative risks, hazard ratios, subdistribution hazard ratios and geometric-mean ratios as ratios with 95% confidence intervals.

19. Adherence and protocol deviations

The intervention follows the overarching protocol. For conservative oxygen, the lowest possible F_IO_2 was used to achieve SpO_2 of at least 91%, with SpO_2 above 94% avoided and an upper alarm limit of 95% whenever supplemental oxygen was administered. For liberal oxygen, oxygen was delivered as directed by the treating clinician with a minimum F_IO_2 of 0.30 during invasive ventilation. Treatment applied in ICU until ICU discharge or day 90, whichever occurred first, and recommenced with ICU readmission during the index hospital admission.

Temporary changes for transport outside ICU and permitted procedures do not constitute protocol deviations. Other concomitant care remained at the treating clinician’s discretion. Protocol deviations will be summarized by assigned group as participants affected and, where recorded, episodes and reasons. Categories can overlap. Participants remain in their allocated groups despite protocol deviations.

Receipt requires purposeful implementation of the assigned oxygen strategy at some point. Similarity of measured oxygen values to a target does not establish receipt. A strategy withheld throughout ICU admission or never communicated to the bedside team is classified as never received. Initial withholding followed by purposeful implementation counts as receipt. Eligibility and receipt are assessed separately; never being invasively ventilated does not by itself establish non-receipt.

Delivery of the intervention will also be described using the daily oxygen plots and participant exposure measures in Sections 26–27 and the appendix. Achieved oxygen exposure is not itself randomized; later-day comparisons condition on continued observation.

Table 11 describes treatment receipt and deviations, and Figure 4 describes eligibility deviations.

20. Analysis populations and estimand

The main HIE analysis population comprises unique Mega-ROX participants whose final recorded baseline classification is suspected HIE following cardiac arrest and whose study data may be used. Participants are analyzed according to their first randomized allocation.

Ineligibility, treatment withdrawal, non-receipt, crossover and other protocol deviations do not exclude a participant from the main analysis. Withdrawal of treatment alone does not withdraw permission to use data. Participants whose data use is not permitted are excluded as required by their consent status. Participants co-enrolled in LOGICAL are included; a requirement for LOGICAL eligibility or long-term follow-up is not imposed.

The primary treatment-policy estimand is the relative risk, with a corresponding risk difference, of in-hospital all-cause mortality within 90 days in adult ICU patients with baseline suspected HIE assigned to conservative rather than liberal oxygen therapy. Treatment deviations are handled by retaining randomized allocation (i.e. the treatment policy strategy is applied). Verified live index-hospital discharge is a non-event even if discharge was not medically indicated.

The body summary tables in Sections 20 and 26 document the estimand and outcome analyses for this SAP.

The primary observed-outcome analysis is supplemented by an analysis of eligible participants only and of eligible participants who purposefully received their assigned strategy. These populations will be defined using the overarching eligibility and receipt conventions and do not replace the main intention-to-treat comparison.

Outcome-specific collection populations follow the overarching SAP. Primary binary mortality uses data from all jurisdictions, including when outcomes are known without exact timing. Event-time analyses will include data from all jurisdictions with usable timing. Ventilation and direct-home analyses exclude data from SA001 (KAIMARC). All-cause day-90 mortality uses the ANZ registry-coverage population defined by participating site, recruitment period and applicable coverage and residency requirements, independently of linkage success. Eligible participants with unresolved linkage or unknown day-90 vital status remain in completeness reporting and have missing all-cause 90-day mortality outcomes. Structural non-collection is reported separately from missing values within a collection population.

Table 7 identifies outcome collection populations, Table 14 reports availability, and Table 15 cross-classifies initial and final HIE status.

The table below describes the estimands of interest for the primary outcome.

Objective: To determine whether conservative oxygen therapy, compared with liberal oxygen therapy, decreases in-hospital all-cause mortality up to 90 days after randomization in adults with baseline suspected HIE following cardiac arrest.
Estimand: Relative risk, with a corresponding risk difference, of index-hospital all-cause mortality up to day 90 among adult ICU patients with baseline suspected HIE assigned to conservative rather than liberal oxygen therapy.
Treatment: Conservative oxygen uses the lowest possible FIO_2 to achieve SpO_2 of at least 91%, avoiding SpO_2 above 94% and using an upper alarm limit of 95% when supplemental oxygen is administered. Liberal oxygen follows clinical direction with a minimum FIO_2 of 0.30 during invasive ventilation. The full intervention is described in Section 19 and the protocols [3,4].

ESTIMAND	ANALYSIS
Target population: Adult ICU patients receiving invasive mechanical ventilation with suspected HIE after cardiac arrest at baseline.	**Analysis set**: Unique participants with final recorded baseline suspected HIE-Yes and permission to use study data, considering only the first randomized allocation. Conservative oxygen is the treatment group and liberal oxygen the comparator. LOGICAL participants remain included.
Variable: All-cause death during the index hospital admission on or before day 90 after randomization.	**Outcome measure**: Index-hospital mortality. Verified live discharge or transfer from the index hospital by day 90, or documented survival in that hospital at day 90, is a non-event. Known binary outcomes are retained when exact timing is missing.
Handling of intercurrent events: - Participants remain in their randomized groups despite ineligibility, non-receipt, crossover or other deviations (treatment-policy strategy). - Patient discharge not medically indicated: patients will be defined as alive if discharged from the hospital even if it is not medically indicated (treatment policy strategy).	**Handling of missing data**: Observed primary outcomes are used. Whenever primary outcomes are missing, both extreme best–worst and worst–best scenarios are considered. Data will be imputed with twenty imputations if either the best-worst or worst-best scenario changes the primary two-sided 5% inference, as defined in Section 31. Suitable overarching imputations are reused if available; otherwise, imputation is restricted to the final-baseline HIE-Yes cohort. **Supporting analyses**: 1. Eligible participants only; 2. eligible participants who purposefully received their assigned strategy; 3. final HIE-Yes restricted to those patients with original HIE-Yes (diagnostic sensitivity 1); 4. all original HIE-Yes (diagnostic sensitivity 2); 5. the expanded final HIE-Yes plus original-Yes/final-No population (diagnostic sensitivity 3). Hypothetical discharge analyses assign death to flagged conservative participants and a non-event to flagged liberal participants, then reverse those assignments. Verified deaths remain deaths.
Population-level summary: Risk ratio comparing conservative with liberal oxygen and risk difference calculated as conservative minus liberal, in percentage points.	**Analysis approach**: Log-binomial regression adjusts for separate final sepsis and non-HIE brain-condition indicators and a random site intercept. A separate identity-link model with the same covariates estimates the risk difference. The constant HIE indicator is omitted. The primary convergence sequence applies (Section 27).

Section 5 Trial Population

21. Screening data

The CONSORT diagram will show the overarching recruitment envelope and how the HIE cohort was identified within it. Available screening counts and reasons for non-enrollment will be reported without implying that a complete trial-wide HIE screening denominator exists where it was not recorded.

Cross-classification of original randomization and final baseline HIE 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

The published HIE criteria require patients to be aged at least 18 years, to be receiving invasive mechanical ventilation in ICU following cardiac arrest, and to have suspected HIE. Suspected HIE was defined as not having obeyed commands after return of spontaneous circulation where there was clinical concern about possible brain injury. The overarching inclusion criterion is unplanned invasive mechanical ventilation; this does not require the ICU admission itself to have been unplanned.

Patients were excluded when enrollment was not considered in their interests by the treating clinician or they had previously been enrolled. The clinical-interest criterion covered situations where either study oxygen regimen was indicated or contraindicated and where death was imminent and inevitable. Enrollment was required within 12 hours of fulfilling eligibility criteria; eligible patients not enrolled within that window were classified as missed for recruitment reporting.

Participants with concomitant sepsis or non-HIE acute brain conditions remain eligible for the HIE analysis. A diagnosis of HIE first arising after randomization will not be used to expand the baseline HIE population. Inadvertently enrolled ineligible patients remain in the main analysis where data use is permitted, with the pre-specified eligible-only sensitivity analysis reported separately.

23. Recruitment

The report will give recruitment dates, participating countries and ICUs, numbers assigned to each oxygen group, unique participants with permitted data use and numbers analyzed for the primary outcome. Flow will distinguish the HIE cohort within the overarching program, consent exclusions, unavailable outcomes and outcome-specific collection restrictions.

Where available, the number of HIE participants also enrolled in LOGICAL will be shown descriptively. LOGICAL status will not determine inclusion in the HIE primary analysis or substitute for the HIE outcome-collection population. Final sample sizes and all results in the mock tables remain placeholders until analysis.

24. Withdrawal and follow-up

Data available before withdrawal will be analyzed where permitted. An instruction to withdraw from allocated treatment will not be equated with withdrawal of permission to retain or use data. Counts and recorded reasons for data withdrawal, incomplete follow-up and missing primary outcomes will be presented by assigned group.

Known binary outcomes can contribute to binary analyses even when precise event timing is missing. Event-time analyses require usable timing and will report their own denominators. Live index-hospital discharge establishes a non-event for primary mortality but does not by itself establish all-cause survival through day 90.

25. Baseline descriptive measures

Baseline characteristics will be summarized as means and standard deviations for approximately symmetric continuous variables, medians and interquartile ranges otherwise, and counts and percentages for categorical variables. No significance tests will compare baseline characteristics between allocations. Each summary will report its observed denominator and missing count. Clinically

meaningful imbalances for additional adjustment will be selected within the HIE analysis population from summaries with treatment allocation masked before treatment-effect results are examined; selected covariates and their clinical rationale will be documented before fitting the additional models.

Table 1 will describe age, sex, body mass index and preadmission frailty where collected, ICU admission source, hospital- and ICU-admission-to-randomization intervals, APACHE II and SAPS 3 where collected, final overlapping sepsis and non-HIE brain-condition status, COVID-19, pre-randomization oxygenation and LOGICAL participation. Each variable will have its observed denominator and relevant collection limitation.

Baseline oxygenation uses the last arterial blood gas before randomization with its paired F_IO_2. F_IO_2 alone cannot supply a PaO_2/F_IO_2 ratio. PaO_2 will be reported in mmHg and F_IO_2 as a fraction. Post-randomization measurements will not be baseline values. APACHE II will be described where collected; SAPS 3 will be described for patients recruited in Brazil. Neither score will enter adjustment models, and SAPS 3 will not substitute for APACHE II.

Initial rhythm and time to return of spontaneous circulation were not collected across Mega-ROX. They are available only in a LOGICAL subset. These fields, arrest-location subgroups and long-term neurological measurements are not available across the whole HIE cohort.

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

Baseline summaries appear in Table 1. Table 10 will compare ANZ HIE trial participants with other registry admissions at the same participating ICUs during the same recruitment periods. Comparable analyses will also use other registries where feasible, with compatible HIE definitions, unplanned invasive ventilation and other criteria observable in both sources. Trial eligibility will not be inferred from criteria absent from the registry. Each descriptive comparison will be labeled by registry and jurisdiction and apply to the population represented.

Table 3 will compare baseline characteristics of final-baseline HIE participants enrolled in LOGICAL with those verified not enrolled, using unique first allocations and permitted data use. LOGICAL status is determined from recorded enrollment, rather than inferred from eligibility, survival or availability of follow-up. Randomized arms are pooled within each membership group. Country or region, recruitment period and randomized allocation will describe differences in the site and period mix alongside the available HIE baseline fields. Unconfirmed membership will not be treated as non-enrollment; its count will be reported. Summaries will show collection-eligible and observed denominators, missing values and structural non-collection by group, without P values.

Section 6 Analysis

26. Outcome definitions

Outcome	Definition	Population	Principal estimate or test
Primary in-hospital mortality	Index-hospital death on or before day 90; verified live discharge/transfer or documented survival in hospital at day 90 is a non-event.	Final-baseline HIE cohort with permitted data use	Random-site-intercept log-binomial risk ratio and separate identity-link risk difference.
Index-hospital survival	From randomization to in-hospital death; follow-up ends at live discharge/transfer, day 90 or last reliable in-hospital observation.	HIE cohort with usable timing	Log-rank test; supporting Cox hazard ratios.
Live ICU discharge	First live exit from index ICU; death before exit is a competing event. Follow-up ends by day 90.	HIE cohort with usable timing	Treatment test from a Fine–Gray model adjusted for final sepsis and non-HIE indicators, with site-clustered errors.
Live hospital discharge	First live exit from index hospital; death before exit is a competing event. Ongoing admission at day 90 is censored.	HIE cohort with usable timing	Treatment test from a Fine–Gray model adjusted for final sepsis and non-HIE indicators, with site-clustered errors.
Total invasive ventilation hours	Completed index-ICU total, including possible pre-randomization hours and hours before death.	HIE ventilation collection population excluding SA001	Diagnosis-adjusted quantile regression with site-clustered standard errors; conditional median difference.
Direct discharge home	Live direct discharge from index hospital to home by day 90. Death, transfer elsewhere or ongoing admission is a non-success; unknown destination after live discharge is missing.	HIE destination collection population excluding SA001	Random-site-intercept binary risk-ratio model; separate risk difference.
All-cause day-90 mortality	Death by day 90, including after discharge; reliable survival through day 90 establishes a non-event.	Predefined HIE ANZ registry-coverage population	Random-site-intercept binary risk-ratio model; separate risk difference.

27. Analysis methods

Primary and binary secondary outcomes: Risk ratios will be estimated using log-binomial models with treatment, final sepsis status and final non-HIE acute brain-condition status, and a random intercept for site. Risk differences will be estimated in separate binomial identity-link models with the same covariates and site structure. Event counts, observed denominators, group proportions, adjusted risk ratios and risk differences and 95% confidence intervals will be reported. Ratios compare conservative with liberal oxygen and differences are conservative minus liberal. A mortality risk ratio below 1 or a negative mortality risk difference favors conservative oxygen. The primary P value corresponds to the hypothesis test for the treatment effect in the risk-ratio model.

Model convergence: The log-link and identity-link models will each use the first convergent model in the overarching sequence. If the original model fails, the random site intercept will be replaced with site-clustered robust standard errors; next sites with fewer than 10 participants will be combined and the original model refit; next sites with fewer than 20 participants will be combined and the original model refit; next the random-site-intercept model will be fit omitting non-HIE brain status, then omitting sepsis, then omitting both. The link appropriate to the estimand is retained throughout. The actual

model used will be identified. If the sequence fails, the corresponding estimate will be unavailable; an unplanned estimator will not replace it.

Index-hospital survival: Kaplan–Meier curves will be labeled Survival during the index hospitalization, with a two-sided log-rank test supplying the formal secondary comparison. Supporting Cox models will include treatment alone and treatment with sepsis and non-HIE brain status, using site-clustered robust standard errors. Hazard ratios are conservative versus liberal. The proportional-hazards assumption will be assessed using Schoenfeld residuals; departures will be described, with no alternative survival model introduced. If needed, the overarching small-site pooling sequence of fewer than 10 then fewer than 20 participants will be applied and the actual model that was fit will be reported.

Live ICU and hospital discharge: Fine–Gray subdistribution-hazard models will include terms for treatment, sepsis and non-HIE brain status with site-clustered robust standard errors, treating death before the relevant live discharge as the competing event. For each of these outcomes, the P value associated with the hypothesis test of a non-zero treatment effect will be that considered in the Holm-Bonferroni set. Subdistribution hazard ratios above 1 indicate a greater cumulative incidence of live discharge with conservative oxygen. Cumulative incidence functions for live discharge and competing death will be displayed. A median time to live discharge will be reported only if the relevant live-discharge cumulative incidence reaches 50%; otherwise it will be reported as not reached. The same small-site pooling sequence as applied to the index-hospital survival outcome applies if needed.

Total ventilation hours: Quantile regression of completed recorded hours will include terms for treatment, sepsis and non-HIE brain status, with site-clustered robust standard errors, using qreg2 in Stata or an equivalent implementation. The treatment coefficient is the adjusted conditional median difference in recorded hours and provides the formal ventilation comparison (i.e. the P value of the associated test statistic will be included in the Holm-Bonferroni set). Patients with zero hours of ventilation will be included in this analysis. Pre-randomization ventilation time will not be subtracted.

Observed completed durations: Additional quantile regressions will compare completed ICU and hospital lengths from randomization to the recorded episode end or death, using all available follow-up, including beyond day 90. These supporting resource-use analyses will include the same diagnostic covariates and site-clustered standard errors. Patients still in the ICU or hospital at the last available follow-up will be right-censored at that time. Censored elapsed times will not be treated as completed durations in the quantile or log-linear models; their numbers and available follow-up will be reported by allocation. Group medians and quartiles, observed denominators, missingness and episode survival status will be reported.

Geometric means: Positive completed ventilation hours and ICU and hospital durations will also be analyzed using log-linear regression with terms for treatment and the two varying diagnostic indicators, with site-clustered robust standard errors. Exponentiated treatment coefficients give conservative-to-liberal ratios of geometric means. Group geometric means and 95% confidence intervals will be reported. Zero durations will be counted separately and excluded only from the logarithmic analyses. Summaries stratified by survival to the end of the relevant episode are descriptive post-randomization summaries; ventilation survival strata use survival to ICU discharge.

Direct discharge home and all-cause day-90 mortality: The binary risk-ratio and risk-difference methods above will be used within the respective collection populations. Known mortality outcomes will not be discarded solely for missing exact dates. The ANZ all-cause analysis will report the number eligible for registry ascertainment and the number with successful linkage and known vital status. No all-cause outcome will be imputed outside the jurisdictions in which it was collected. An ANZ registry-based all-cause survival plot is a supporting display, separately labeled from the all-site index-hospital curve. 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.

Oxygen exposure: For each participant and metric, daily threshold hours and their corresponding daily total hours will be summed over days on which both were recorded and the measure applied. Percentage exposure is 100 times the summed threshold hours divided by the summed corresponding

observed hours; daily percentages will not be averaged. SpO_2 metrics use Total SpO_2 Hours and room-air metrics use Total FIO_2 hours. Missing threshold hours will not be set to zero. A percentage is unavailable where the summed denominator is zero; recorded zero threshold hours with a positive denominator remain included.

Median recorded hours and percentages at SpO_2 at least 97%, SpO_2 below 88% and FIO_2 0.21 will be compared using quantile regression with site-clustered robust standard errors. Any PaO_2 below 60 mmHg uses the separate daily Lowest fields; any PaO_2 above 100 mmHg uses the separate daily Highest fields. Each binary denominator is participants with at least one observation in the relevant field. These comparisons use log-binomial models with a random site intercept, reporting events, observed denominators, risk ratios and 95% confidence intervals. They are outside the secondary multiplicity family.

Daily oxygen plots: A participant's daily mean is the average of available scheduled 06:00, 12:00, 18:00 and 24:00 readings. The separate Highest and Lowest fields provide the daily extremes; extrema among scheduled readings will not replace them. Group means give participants equal weight and will be plotted with standard errors and contributing participant counts for every day, group and measure. FIO_2 scheduled and extreme fields apply while ventilated; the FIO_2 0.21 duration block includes time after extubation; the PaO_2 block has no ventilation restriction. Values are not imputed after death, first ICU discharge or the relevant end of collection.

The corresponding output shell tables are Tables 5–6 and 13, the oxygen definitions are in Table 9, and the supporting completed-duration summaries are in Table 18. Daily oxygen plots are Figures 5–6; Figure 7 is the separately labeled ANZ all-cause survival display.

Table 4 will describe the primary and secondary HIE outcomes and completed ICU and hospital durations by recorded LOGICAL enrollment versus verified non-enrollment, pooling randomized arms. It uses the same final-baseline HIE population, definitions, time origins and outcome-specific collection restrictions as the randomized comparisons. Group-specific collection-eligible and observed denominators, missingness and structural non-collection will be shown; survival summaries require usable timing. Supporting ICU and hospital durations use all available episode follow-up, including beyond day 90, with completed and right-censored episode counts shown separately in each LOGICAL membership group. Live-exit summaries will use counts and cumulative incidence with death competing; a median will be reported only if the live-discharge cumulative incidence reaches 50%. ANZ all-cause day-90 mortality remains confined to the predefined registry-coverage population, with eligible, linked and known-status counts shown separately in each membership group. These descriptive comparisons introduce no participation-effect estimate, hypothesis test, treatment interaction or imputation solely for this table. LOGICAL long-term neurological or functional outcomes are not added to the remaining HIE cohort.

28. Adjustment for covariates

The primary adjustment set is final sepsis and final non-HIE brain-condition status, entered as separate indicators to represent overlapping conditions, with a random site intercept. The constant HIE indicator is omitted. Supporting analyses of the primary outcome will also include terms for age and sex, followed by baseline covariates with clinically meaningful imbalances. These covariates will be selected within the HIE analysis population from allocation-masked summaries before treatment-effect results are examined, and their clinical rationale documented before fitting the models. APACHE II and SAPS 3 will not be adjustment covariates because their measurement windows may extend beyond randomization.

Initial rhythm, time to return of spontaneous circulation and other LOGICAL-only arrest variables are not available trial-wide and will not be required HIE covariates.

If an additionally adjusted model fails, the overarching convergence sequence will apply, with additional covariates omitted one at a time in the order clinically imbalanced variables, age, then sex, followed by pairs in the same order if required. The actual terms, site handling and denominator will be reported. Variable selection will not use baseline P values or treatment findings. The primary analysis will continue to use all HIE participants with an observed primary outcome.

29. Sensitivity analyses

The primary mortality analysis will be repeated in eligible participants and in eligible participants who purposefully received the allocated strategy. The definition of treatment receipt is provided in Section 19. Minor deviations or failure to achieve target oxygen values do not by themselves change the analyzed allocation of a patient or exclude a patient from analyses.

The two pre-specified non-medically-indicated-discharge scenarios will be applied to participants flagged contemporaneously as discharged from ICU to home while ongoing care remained medically indicated. In the first scenario, conservative-oxygen participants are assigned death and liberal-oxygen participants a non-event; the assignments are reversed in the second. Verified deaths remain deaths. Flagged participants with otherwise missing outcomes receive the scenario assignment. Risk ratios and risk differences will be reported.

Whenever primary outcomes are missing, worst–best and best–worst outcome scenarios will be analyzed as described in Section 31. Multiple imputation follows the pre-specified trigger in Section 31, reusing suitable overarching imputations if available; otherwise, imputation is restricted to the final-baseline HIE-Yes cohort. These analyses address missing outcomes and are distinct from the non-medically-indicated-discharge scenarios.

Diagnostic sensitivity 1 will repeat the primary analysis in the final baseline HIE-Yes cohort restricted to participants whose original randomization HIE field was also Yes. This retains the previously planned restriction and assesses the influence of HIE cases added after an original No response. Diagnostic sensitivity 2 will include all unique participants with original HIE-Yes and permitted data use, including those subsequently classified as HIE-No. Diagnostic sensitivity 3 will use the expanded population comprising final baseline HIE-Yes plus original HIE-Yes/final HIE-No participants. All three analyses retain allocated treatment and use the primary sepsis/non-HIE adjustment and convergence sequence. Counts, outcomes and overlap will be reported by allocation. These supporting analyses extend the published HIE plan and are outside the Holm family.

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 equal to the reciprocal of each participant's actual probability of receiving the assigned regimen, with categorical randomization epoch included. Epochs are defined by implementation dates of updated probabilities. For overlapping conditions and corrected diagnoses, weights use the probability actually applied under the original classification and hierarchy. Risk ratios and risk differences retain the conservative-versus-liberal orientation.

These sensitivity analyses are supporting and outside the secondary Holm–Bonferroni family.

The planned primary sensitivity outputs are in Table 12; Table 15 supplies the initial-versus-final HIE classification counts.

30. Subgroup analyses

The pre-specified HIE subgroup comparison is admission to ICU from the emergency department versus admission from elsewhere. Admission source must be observed in a jurisdiction where it was collected. Missing admission source will not be imputed, whether the source was uncollected or incompletely recorded, and will not be assigned to elsewhere. The number in the collection population and the number with a usable subgroup category will be shown.

The primary risk-ratio model will include treatment, subgroup, treatment-by-subgroup interaction, final sepsis and non-HIE brain status, with a random site intercept. Treatment effects and 95% confidence intervals within each subgroup and the interaction P value will be reported. Where an estimate cannot be obtained, the primary convergence principles will be applied and any remaining unavailable contrast identified.

This interaction is exploratory and is not part of the secondary multiplicity family. Differences in subgroup-specific significance will not be used as evidence of interaction.

The pre-specified admission-source subgroup appears in Figure 2 alongside the index-hospital survival display.

31. Missing data

For each outcome and important baseline or subgroup variable, the collection-eligible denominator, observed denominator and number missing will be reported by allocation. Structural non-collection, unlinked registry data, unknown outcome and missing event timing will be distinguished where the source permits. Only participants within the relevant collection population are eligible for that outcome's missing-data assessment.

The primary analysis uses observed primary mortality outcomes. If any are missing, the worst–best scenario assigns death by day 90 in the index hospital to all missing conservative-group outcomes and a non-event to all missing liberal-group outcomes; best–worst makes the opposite assignments. A non-event includes live discharge and documented survival in the index hospital at day 90.

Multiple imputation with 20 datasets will be undertaken if either extreme scenario changes the primary inference at the two-sided 5% level. A change means the primary treatment test moves between $P<0.05$ and $P\geq0.05$, or a statistically significant result favors the opposite group. Complete-case and imputed results will both be shown when imputation is required. If primary outcomes are complete within a specified analysis population, no primary-outcome imputation or extreme-scenario analysis is required for that analysis.

Multiple imputation, when required, will reuse suitable imputed datasets from the overarching Mega-ROX analysis if available. If suitable overarching datasets are unavailable, the HIE-specific procedure below will generate 20 datasets within the final-baseline HIE-Yes cohort, restricted to the relevant outcome-specific collection population. First allocation and data-use permissions apply. Missing baseline auxiliary values are filled using center-specific means, or modes for categorical variables, as specified in the overarching SAP. Baseline variables will be compared between participants with and without primary outcomes using t tests or Wilcoxon rank-sum tests for continuous characteristics and chi-squared tests for categorical characteristics. These comparisons help select auxiliary predictors together with clinical knowledge and the analysis covariates; they are not treatment-group balance tests.

For the HIE-specific procedure within the final-baseline HIE-Yes cohort and relevant outcome-specific collection population, outcomes will be imputed separately by allocated group using analysis covariates and relevant baseline predictors of outcome or missingness. Binary outcomes use logistic regression without site because of possible perfect prediction in small sites. Continuous-outcome models 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 structurally uncollected outcome will be imputed.

When required, ANZ all-cause day-90 mortality will use suitable overarching imputations if available. Otherwise, it will be imputed using logistic regression within the intersection of the final-baseline HIE-Yes cohort and the intended ANZ registry-coverage population. Missing destination or duration values will be distinguished from structural non-collection. Outcomes will not be imputed in jurisdictions or periods where they were not collected.

Density plots for continuous variables and proportion plots for binary variables will compare imputed and observed distributions. For analysis of imputed datasets, a method is deemed successful if it converges in at least 75% of datasets. If the selected model fails in more than one quarter, the pre-specified fallback sequence is applied. The number of datasets fitted and any omissions will be reported, with available estimates combined using Rubin's rules. If the sequence provides no estimate, the result will be reported as unavailable.

Secondary clinical outcomes will be analyzed using observed outcomes within their collection populations. Imputation, when required, will reuse suitable overarching datasets if available; otherwise, the outcome-specific procedures above will be applied within the final-baseline HIE-Yes cohort and

relevant collection population. The primary-outcome trigger in this section does not imply routine imputation of every secondary outcome.

Outcome collection denominators, observed values and missingness appear in Table 14.

32. Harms

As in the overarching SAP, 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. Reports describe reported events and cannot estimate the incidence of all complications.

Table 16 will summarize all adverse-event reports recorded for the principal HIE population under the original Mega-ROX reporting procedures through database lock. Participant counts, serious reports, total reports, recorded relatedness and unresolved assessments will be presented by allocation. Each participant is counted once in participant-based summaries and may contribute multiple reports. The original reporting scope and available event dates will accompany the summary. Safety comparisons will be descriptive. Recorded categories will be reproduced without inferring unreported diagnoses; absence of a report does not establish absence of harm.

Physiological exposure metrics such as recorded hypoxemia are reported separately from adverse-event reports. No new clinical event ascertainment or new long-term neurological safety outcome is assumed for HIE.

Reported adverse-event summaries appear in Table 16.

33. Statistical software and code

Stata version 19 or later or R version 4.4.1 or later will be used, following the overarching SAP. Exact versions and packages will be recorded. Core models correspond to binomial log-link and identity-link models with random site intercepts; Cox models and Fine–Gray models with cluster-robust standard errors; quantile regression with standard errors allowing for clustering by site; and log-linear duration regression with cluster-robust standard errors.

Treatment coding will consistently produce conservative-versus-liberal ratios and conservative-minus-liberal differences. Estimates, interval units, model population and formal or supporting test status will be retained in the analysis output. Illustrative code and the full fallback details in the overarching SAP apply with this HIE-specific adjustment set.

Illustrative Stata specifications use TreatmentGroup=1 for conservative oxygen and TreatmentGroup=0 for liberal oxygen. Final sepsis and non-HIE brain-condition status enter as separate indicators; the constant HIE indicator is omitted.

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

Final variable names and syntax will be verified against the approved definitions. The specified convergence fallbacks, outcome-specific populations and site handling apply to these illustrative models.

34. Modifications from published SAP

The baseline HIE population, conservative-versus-liberal hypothesis, index-hospital mortality endpoint and emergency-department-versus-elsewhere subgroup are retained from the 2024 HIE protocol. Section 17 specifies the conditional Holm family. LOGICAL participants remain included. The appendix specifies planned HIE tables and figures.

The overarching methods now specify random site intercepts in the primary binary models, separate identity-link risk differences, the original convergence sequence, age and sex adjustment without illness-severity scores, an inverse-probability-weighted analysis with epoch, and the revised primary missing-outcome imputation trigger. These details replace or expand the less detailed published specification.

The revised ventilation endpoint is completed total ventilation hours, compared using quantile regression. Supporting completed-duration and geometric-mean analyses use the recorded ventilation total and completed ICU or hospital episode lengths, using all available index-episode follow-up, including beyond day 90. Ongoing ICU or hospital episodes at last follow-up will be reported as censored rather than as completed durations. The formal 90-day live-discharge event-time analyses remain separate.

The all-site survival display is restricted to index-hospital survival. The separate ANZ all-cause survival display is subject to the death registry linkage requirement in Section 27. All-cause day-90 mortality is restricted to ANZ registry coverage; ventilation and destination analyses exclude SA001. These collection restrictions and denominators follow the overarching SAP.

Oxygen summaries now use the actual CRF fields, separate recorded daily Highest and Lowest values, observed metric-specific hours, and participant counts. SpO_2 threshold hours are not PaO_2 threshold hours. The published table's primary-adjustment footnote incorrectly names HIE instead of non-HIE brain status; this is corrected to match the HIE protocol's main analysis text.

Alignment with overarching SAP version 2.0 dated 9 November 2026 clarifies data-source precedence, allocation-masked covariate selection, implementation-date epochs, conditional outcome-specific imputation with reuse of suitable overarching datasets if available and otherwise within the final-baseline HIE-Yes cohort, registry coverage and descriptive reported-event summaries. The estimand and outcome summaries in Sections 20 and 26 and the HIE-specific illustrative model code make these shared methods explicit. APACHE II is restored as a descriptive measure where collected. The three supporting diagnostic sensitivities retain the original-and-final Yes restriction and add original-Yes and expanded-cohort analyses. A comparison in the applicable Holm–Bonferroni family retains its place if a valid P value cannot be obtained, including failure to produce the required treatment-effect estimate or standard error. P=1 is used solely for adjustment. Failure of a supporting effect-estimation model does not replace an available pre-specified formal test.

Descriptive baseline and outcome comparisons by recorded LOGICAL enrollment will be presented alongside the other planned analyses. These comparisons do not alter the randomized estimands, pre-specified analyses or secondary multiplicity family.

35. References

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

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

3. Young PJ, Al-Fares A, Aryal D, et al. Protocol and statistical analysis plan for the mega randomised registry trial comparing conservative vs. liberal oxygenation targets in adults in the intensive care unit with suspected hypoxic ischaemic encephalopathy following a cardiac arrest (Mega-ROX HIE). Critical Care and Resuscitation. 2024;26:87–94. doi:10.1016/j.ccrj.2024.03.004.

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

5. LOGICAL Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative Oxygen for Unresponsive Patients after Cardiac Arrest. N Engl J Med. 2026;395:571–581. doi:10.1056/NEJMoa2513814.

6. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020;382:989–998. doi:10.1056/NEJMoa1903297.

7. Australian New Zealand Clinical Trials Registry. The Mega Randomised Registry Trial Comparing Conservative vs. Liberal OXygenation Targets. ACTRN12620000391976. Updated 13 December 2025. Accessed 2 November 2026. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379432&isReview=true.

36. Planned tables

The planned tables present randomized treatment effects and descriptive analyses with outcome-specific populations and denominators. Ratios compare conservative with liberal oxygen, and differences are conservative minus liberal. Table 5 presents the oxygen exposure metrics; Table 9 gives their definitions and ascertainment.

Table 1: Characteristics of the Patients at Baseline*

Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Age — yr	[XX.X ± XX.X]	[XX.X ± XX.X]
Male sex — no. (%)	[n/N (%)]	[n/N (%)]
Body-mass index — kg/m²	[XX.X ± XX.X]	[XX.X ± XX.X]
Clinical Frailty Scale — median (IQR)	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]
Emergency department admission — no. (%)	[n/N (%)]	[n/N (%)]
Hospital ward admission — no. (%)	[n/N (%)]	[n/N (%)]
Transfer from another ICU — no. (%)	[n/N (%)]	[n/N (%)]
Transfer from another hospital, excluding ICU — no. (%)	[n/N (%)]	[n/N (%)]
Operating theater following surgery — no. (%)	[n/N (%)]	[n/N (%)]
Time from hospital admission to randomization — hr	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]
Time from ICU admission to randomization — hr	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]
SAPS 3 score — Brazil only	[XX.X ± XX.X]	[XX.X ± XX.X]
APACHE II score — where collected	[XX.X ± XX.X]	[XX.X ± XX.X]
Coexisting sepsis — no. (%)	[n/N (%)]	[n/N (%)]
Coexisting non-HIE brain injury or condition — no. (%)	[n/N (%)]	[n/N (%)]
Confirmed or suspected COVID-19 — no. (%)	[n/N (%)]	[n/N (%)]
Baseline F_IO_2 — fraction	[XX.X ± XX.X]	[XX.X ± XX.X]
Baseline PaO_2 — mmHg	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]
Baseline PaO_2/F_IO_2 ratio — mmHg	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]
Participation in LOGICAL — no. (%)	[n/N (%)]	[n/N (%)]

* Values are mean ± SD, median (IQR), or n/N (%), with variable-specific observed denominators and missing counts. Body mass index and preadmission frailty are summarized where collected. APACHE II is descriptive where collected; SAPS 3 is descriptive for Brazil. Neither score is an adjustment covariate. LOGICAL participation is descriptive and does not restrict HIE inclusion.

HIE denotes hypoxic ischemic encephalopathy; ICU, intensive care unit; IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS 3, Simplified Acute Physiology Score 3; LOGICAL, the nested long-term follow-up trial.

Table 2: Randomized Clinical Outcomes in Mega-ROX HIE*

Outcome	Conservative oxygen	Liberal oxygen	Adjusted effect (95% CI)	Risk difference, pp (95% CI)	P value*
Primary outcome					
Index-hospital death by day 90	[n/N (%)]	[n/N (%)]	[RR; 95% CI]	[pp; 95% CI]	[P_primary]
Secondary outcomes					
Index-hospital survival, deaths/N	[deaths/N]	[deaths/N]	[Cox HR; 95% CI]	—	[P_Holm1]
Live ICU discharge by day 90	[n/N (%)]	[n/N (%)]	[SHR; 95% CI]	—	[P_Holm2]
Live hospital discharge by day 90	[n/N (%)]	[n/N (%)]	[SHR; 95% CI]	—	[P_Holm3]
Completed total invasive ventilation, hr	[median (IQR)]	[median (IQR)]	[median difference; 95% CI]	—	[P_Holm4]
Direct discharge home by day 90	[n/N (%)]	[n/N (%)]	[RR; 95% CI]	[pp; 95% CI]	[P_Holm5]
ANZ all-cause death by day 90	[n/N (%)]	[n/N (%)]	[RR; 95% CI]	[pp; 95% CI]	[P_Holm6]

* The primary P value is the raw risk-ratio-model treatment P value. Secondary P values are adjusted within the applicable Holm family in Section 17. Raw P values and formal tests are in Table 17. If ANZ all-cause day-90 mortality reporting is deferred, omit its row and adjust the other five outcomes. All effect intervals are pointwise 95% intervals. The Cox HR is supporting; the survival log-rank P value enters the Holm family. RR denotes risk ratio; SHR, Fine–Gray subdistribution hazard ratio; pp, percentage points; IQR, interquartile range. Model adjustment remains final sepsis and non-HIE brain-condition status with the specified site handling. Table 6 gives the expanded outcome estimates and denominators; Table 13 gives ANZ coverage and mortality details, subject to the death registry linkage requirement in Section 27. These displays do not create additional formal comparisons.

Table 3: Baseline Characteristics by Recorded LOGICAL Enrollment*

Characteristic	Enrolled in LOGICAL N=[N]	Verified not enrolled N=[N]	LOGICAL availability* C / O / M / NC	Non-LOGICAL availability* C / O / M / NC
Country or region: [category] — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Recruitment period: [epoch/date range] — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Randomized allocation: conservative — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Randomized allocation: liberal — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Age — yr	[XX.X ± XX.X]	[XX.X ± XX.X]	[N / n / n / n]	[N / n / n / n]
Male sex — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Body-mass index — kg/m²	[XX.X ± XX.X]	[XX.X ± XX.X]	[N / n / n / n]	[N / n / n / n]
Clinical Frailty Scale — median (IQR)	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N / n / n / n]	[N / n / n / n]
Emergency department admission — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Hospital ward admission — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Transfer from another ICU — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Transfer from another hospital, excluding ICU — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Operating theater following surgery — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Time from hospital admission to randomization — hr	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N / n / n / n]	[N / n / n / n]
Time from ICU admission to randomization — hr	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N / n / n / n]	[N / n / n / n]
SAPS 3 score — Brazil only	[XX.X ± XX.X]	[XX.X ± XX.X]	[N / n / n / n]	[N / n / n / n]
APACHE II score — where collected	[XX.X ± XX.X]	[XX.X ± XX.X]	[N / n / n / n]	[N / n / n / n]
Coexisting sepsis — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Coexisting non-HIE brain injury or condition — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Confirmed or suspected COVID-19 — no. (%)	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Baseline F_IO_2 — fraction	[XX.X ± XX.X]	[XX.X ± XX.X]	[N / n / n / n]	[N / n / n / n]
Baseline PaO_2 — mmHg	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N / n / n / n]	[N / n / n / n]
Baseline PaO_2/F_IO_2 ratio — mmHg	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N / n / n / n]	[N / n / n / n]

* Both randomized arms are pooled within each group. LOGICAL status is determined from recorded enrollment, rather than inferred from eligibility, survival or availability of follow-up; the comparator is verified non-enrollment. The final-baseline HIE cohort uses unique first allocations and permitted data use. HIE cohort N=[N]; unconfirmed LOGICAL status n=[n], reported separately and not assigned to non-enrollment. C / O / M / NC are collection-eligible N, observed n, missing n within C, and structurally not collected n, separately for each group and variable. Recruitment epochs and country/region categories will be specified from the recorded data. Summaries use the available HIE baseline fields only; APACHE II is descriptive where collected and SAPS 3 for Brazil. Initial rhythm, time to ROSC and arrest location are not assumed collected across HIE. No hypothesis tests or causal participation effects are planned.

Table 4: HIE Outcomes by Recorded LOGICAL Enrollment*

Outcome or coverage measure	Enrolled in LOGICAL N=[N]	Verified not enrolled N=[N]	LOGICAL availability* C / O / M / NC	Non-LOGICAL availability* C / O / M / NC
Index-hospital death by day 90	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
Index-hospital survival	[deaths/N; KM survival at day 90 (95% CI)]	[deaths/N; KM survival at day 90 (95% CI)]	[N / n / n / n]	[N / n / n / n]
Live ICU discharge by day 90	[live exits/N; CIF median (95% CI) or not reached]	[live exits/N; CIF median (95% CI) or not reached]	[N / n / n / n]	[N / n / n / n]
Live hospital discharge by day 90	[live exits/N; CIF median (95% CI) or not reached]	[live exits/N; CIF median (95% CI) or not reached]	[N / n / n / n]	[N / n / n / n]
Completed total invasive ventilation, hr	[median (IQR)]	[median (IQR)]	[N / n / n / n]	[N / n / n / n]
Direct discharge home by day 90	[n/N (%)]	[n/N (%)]	[N / n / n / n]	[N / n / n / n]
ANZ registry-coverage eligible participants	[N]	[N]	—	—
ANZ registry-linked participants	[n/N eligible (%)]	[n/N eligible (%)]	—	—
ANZ participants with known day-90 vital status	[n/N eligible (%)]	[n/N eligible (%)]	—	—
ANZ all-cause death by day 90	[n/N known (%)]	[n/N known (%)]	[N / n / n / n]	[N / n / n / n]
Completed ICU duration, days	[completed n; right-censored n; median (IQR)]	[completed n; right-censored n; median (IQR)]	[N / n / n / n]	[N / n / n / n]
Completed hospital duration, days	[completed n; right-censored n; median (IQR)]	[completed n; right-censored n; median (IQR)]	[N / n / n / n]	[N / n / n / n]

* Membership, pooled randomized arms, cohort restrictions and C / O / M / NC follow Table 3. Unconfirmed membership is reported separately. Outcomes retain the definitions and collection populations in Section 26. Survival O is the number with usable event/censoring timing; missing timing is reported separately from known death status. Live exits include transfers; death before exit competes. CIF medians are reported only when the live-discharge cumulative incidence reaches 50%, and are not medians among discharged survivors. Ventilation is completed total index-ICU hours, potentially including pre-randomization time and hours before death. Completed ICU/hospital durations use all available follow-up from randomization to the recorded episode end or death, including beyond day 90. For these rows, O is the number of completed episodes. Ongoing episodes are right-censored at last follow-up and reported separately in each membership group; they are excluded from completed-duration summaries and are not counted as sporadically missing completed durations. Ventilation and direct-home outcomes exclude SA001 (KAIMARC). All-cause day-90 mortality uses only the predefined ANZ registry-coverage population; LOGICAL enrollment or follow-up elsewhere, including Ireland, does not confer ANZ coverage. Eligible, linked and known-status counts are distinct; live hospital discharge alone does not establish day-90 survival. Comparisons are descriptive, with no between-membership effect estimate, P value, interaction test or imputation solely for this display. LOGICAL-specific long-term neurological/functional outcomes are not compared with the remaining HIE cohort. Reporting of ANZ all-cause day-90 mortality is subject to the death registry linkage requirement in Section 27.

Table 5: Oxygen Exposure Metrics*				
Oxygen exposure metric	Conservative oxygen (n=XXX)	Liberal 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)	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	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, conservative minus liberal; 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 6: Primary and Secondary Outcomes*			
Outcome	**Conservative oxygen N=[N]**	**Liberal oxygen N=[N]**	**Estimate (95% CI)**
Primary outcome			
Death during the index hospitalization within 90 days, no. (%)	[n/N (%)]	[n/N (%)]	Risk ratio [X.XX; 95% CI]†
			Risk difference [X.X percentage points; 95% CI]
Secondary outcomes			
Completed total invasive ventilation hours‡			
Number with recorded completed duration	[N]	[N]	
Median (IQR), hours	[median (IQR)]	[median (IQR)]	Conditional median difference [hours; 95% CI]‡
Days to live ICU discharge‡			
Number of patients	[N events]	[N events]	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subdistribution HR [95% CI]‡
Days to live hospital discharge‡			
Number of patients	[N events]	[N events]	
CIF median time, days (95% CI), or not reached	[median (95% CI) / not reached]	[median (95% CI) / not reached]	Subdistribution HR [95% CI]‡
Discharged directly home from hospital, no. (%)	[n/N (%)]	[n/N (%)]	Risk ratio [X.XX; 95% CI]§
			Risk difference [X.X percentage points; 95% CI]
Survival during the index hospitalization, deaths/N	[deaths/N]	[deaths/N]	[Hazard ratio; 95% CI]¶
All-cause death by day 90 in the ANZ registry-coverage population, no. (%)	[n/N (%)]	[n/N (%)]	Risk ratio [X.XX; 95% CI]
			Risk difference [X.X percentage points; 95% CI]

* Primary P=[P] is from the risk-ratio model. All 95% confidence intervals are pointwise. Table 17 gives the raw and Holm-adjusted P values for the applicable family. Table 13 gives ANZ all-cause day-90 mortality if the linkage requirement in Section 27 is met.

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

‡ Total ventilation hours will include any pre-randomization hours and hours before death and will be compared using adjusted quantile regression with site-clustered standard errors. Fine–Gray models for live ICU/hospital exit will adjust for the same diagnoses with site-clustered errors and death competing. A CIF median will be reported only if live discharge reaches 50%.

§ Direct-home analyses will exclude SA001 (KAIMARC); 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.

Table 7: 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; SA002 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 8: Randomization Ratios Applied in the Mega-ROX HIE Trial

Allocation epoch (start date)	HIE 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: [ratio] None: [ratio]
After 1,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 8,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 16,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 24,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]
After 32,000 participants [date]	[n–n]	[hierarchy]	HIE: [ratio] Sepsis: [ratio] Other brain condition: [ratio] None: [ratio]

Allocation records will provide implementation dates, trial-ID boundaries, hierarchy and liberal-to-conservative ratios for each epoch and governing diagnostic group represented in HIE. Weights use each participant's actual allocation probability under the classification and hierarchy applied at randomization. Corrected HIE diagnoses do not redefine those probabilities. This allocation-ratio convention is distinct from the conservative-versus-liberal orientation of treatment-effect estimates.

Table 9: 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 10: Representativeness of HIE Trial Participants*

Characteristic	HIE trial cohort	Other compatible registry admissions	N (trial / registry)
Age — yr	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N] / [N]
Male sex — no. (%)	[n/N (%)]	[n/N (%)]	[N] / [N]
Clinical Frailty Scale	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N] / [N]
Emergency department admission — no. (%)	[n/N (%)]	[n/N (%)]	[N] / [N]
Coexisting sepsis — no. (%)	[n/N (%)]	[n/N (%)]	[N] / [N]
Coexisting non-HIE brain condition — no. (%)	[n/N (%)]	[n/N (%)]	[N] / [N]
Total invasive ventilation hours	[XX.X (XX.X to XX.X)]	[XX.X (XX.X to XX.X)]	[N] / [N]
Death during index hospitalization by day 90 — no. (%)	[n/N (%)]	[n/N (%)]	[N] / [N]

* The ANZ comparison will use HIE trial participants and other ANZICS Adult Patient Database admissions at the same participating ICUs during their recruitment periods. Other registry comparisons will be presented separately where feasible using compatible HIE definitions, unplanned invasive ventilation and criteria observable in both sources. Eligibility will not be inferred from unrecorded criteria. Each comparison will identify its registry and jurisdiction. Observed and missing denominators will be reported; comparisons are descriptive without baseline significance tests.

Table 11: Protocol Deviations and Delivery of Allocated Treatment

Nature of deviation	Conservative oxygen (n=[N])	Liberal oxygen (n=[N])
Allocated treatment never given – no. (%)	xxx (xx.x)	xxx (xx.x)
Any recorded protocol deviation	xxx (xx.x)	xxx (xx.x)
Initial withholding followed by purposeful implementation (received)	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	xxx (xx.x)	Not applicable
Used an FIO2 less than 0.3 during mechanical ventilation	Not applicable	xxx (xx.x)

Abbreviations: FIO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, arterial partial pressure of oxygen; SaO2, arterial oxygen saturation; SpO_2, oxygen saturation measured by peripheral pulse oximetry.

Table 12: Supporting Analyses of the Primary Outcome*

Analysis	Conservative events/N	Liberal events/N	Risk ratio (95% CI)	Risk difference, pp (95% CI)
Primary observed-outcome analysis	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Eligible participants only	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Eligible participants who received allocated strategy	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Additional age and sex adjustment	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Additional clinically imbalanced covariates	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Final HIE-Yes restricted to original HIE-Yes	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
All original randomization HIE-Yes participants	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Expanded final HIE-Yes plus original-Yes/final-No	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Non-medically-indicated discharge: conservative dead, liberal alive	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Non-medically-indicated discharge: conservative alive, liberal dead	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Missing outcomes: conservative dead, liberal alive	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Missing outcomes: conservative alive, liberal dead	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Multiple imputation with 20 datasets in final HIE-Yes, if triggered	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]
Inverse-probability weighting with implementation-date epoch	[n/N]	[n/N]	[RR; 95% CI]	[RD; 95% CI]

* Models retain final sepsis and non-HIE brain-condition adjustment and the specified site/convergence sequence. Ratios are conservative relative to liberal; risk differences are conservative minus liberal in percentage points (pp). All intervals are pointwise. The original-and-final HIE-Yes restriction, original-Yes cohort and expanded cohort follow section 29; classification movements are in Table 15. These analyses are supporting and outside the secondary Holm family.

Table 13: All-Cause Mortality by Day 90 in the ANZ Registry-Coverage Population		
Measure	**Conservative oxygen**	**Liberal 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
Primary index-hospital death in the same ANZ population	[n/N (%)]	[n/N (%)]
Supporting index-hospital mortality risk ratio (95% CI)	[RR (95% CI)]	Reference
Supporting index-hospital mortality risk difference, pp (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. Index-hospital mortality in the same ANZ population is a supporting comparison; it does not add another formal secondary test. Reporting of ANZ all-cause day-90 mortality is subject to the death registry linkage requirement in Section 27.

Table 14: Outcome Availability by Randomized Allocation		
Outcome	Conservative oxygen	Liberal 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]
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]
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]

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

Table 15: Original and Final HIE Classifications		
HIE classification	**Conservative oxygen**	**Liberal 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 matrix includes unique parent-trial participants with permitted data use, including those outside the principal final HIE cohort. Final HIE-Yes defines the principal cohort; original-Yes, concordant-Yes and expanded populations follow section 29. Cohort membership and primary-outcome sensitivity estimates will be presented in Table 12.

Table 16: Reported Adverse Events		
Measure	Conservative oxygen	Liberal 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 17: 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.

Table 18: Supporting Completed-Duration Analyses*

Duration and stratum	Conservative oxygen	Liberal oxygen	Conditional median difference (95% CI)	Ratio of geometric means (95% CI)
Total invasive ventilation, hours — All completed episodes	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	[median difference; 95% CI]	[GM ratio; 95% CI]
Total invasive ventilation, hours — Survived relevant episode	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	Descriptive	Descriptive
Total invasive ventilation, hours — Died during relevant episode	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	Descriptive	Descriptive
Completed ICU duration, days — All completed episodes	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	[median difference; 95% CI]	[GM ratio; 95% CI]
Completed ICU duration, days — Survived relevant episode	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	Descriptive	Descriptive
Completed ICU duration, days — Died during relevant episode	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	Descriptive	Descriptive
Completed hospital duration, days — All completed episodes	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	[median difference; 95% CI]	[GM ratio; 95% CI]
Completed hospital duration, days — Survived relevant episode	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	Descriptive	Descriptive
Completed hospital duration, days — Died during relevant episode	N [N]; zero [n] median [IQR]; GM [CI]	N [N]; zero [n] median [IQR]; GM [CI]	Descriptive	Descriptive

* ICU and hospital durations use all available follow-up from randomization to the recorded index-episode end or death, including beyond day 90. Ongoing episodes are right-censored at last 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 14). Ventilation uses completed total index-ICU hours and can include pre-randomization time. Zeros remain in quantile analyses and are excluded only from positive-only geometric means. Models adjust for final sepsis and non-HIE brain conditions with site-clustered standard errors. Comparisons within survival strata are descriptive because survival is post-randomization. GM denotes geometric mean; CI, confidence interval.

37. Planned figures

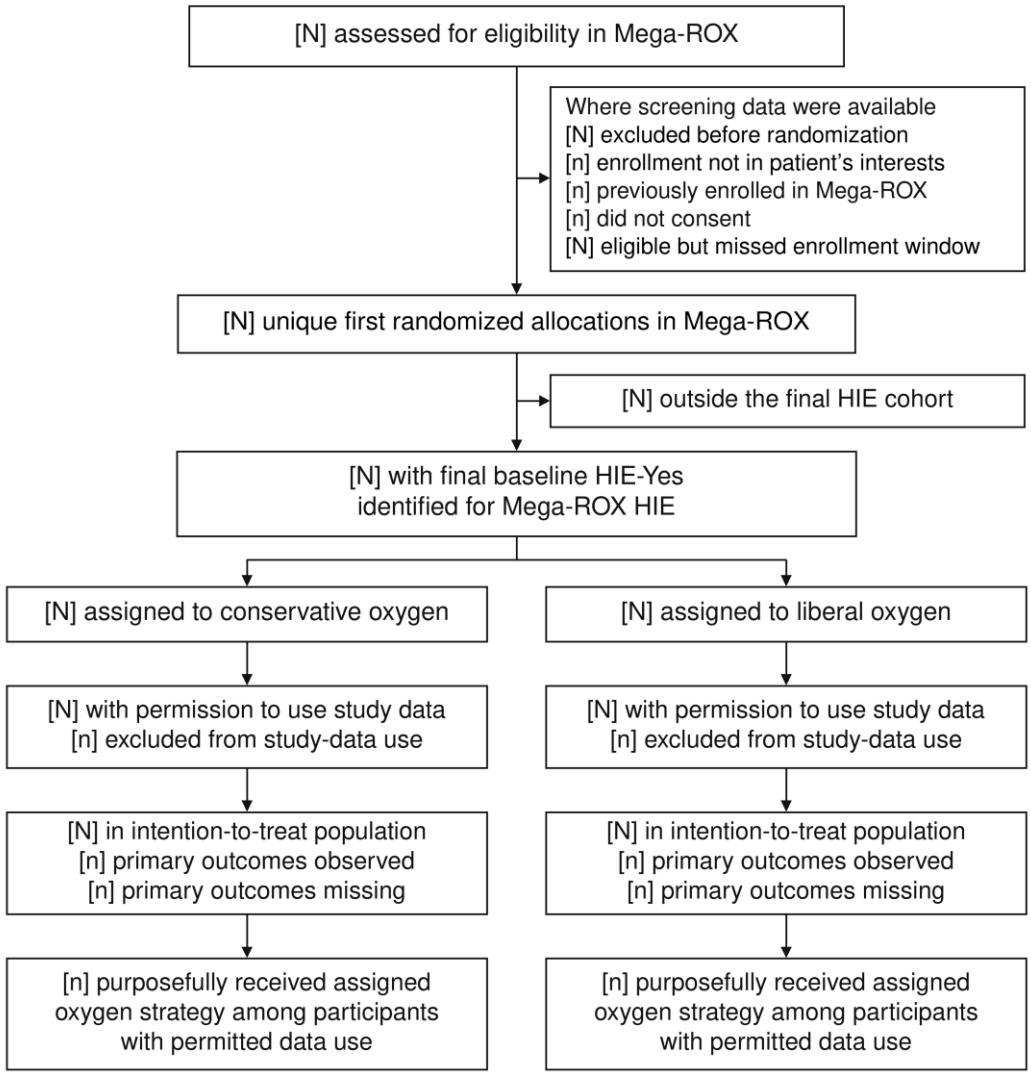


Figure 1. Randomization and Follow-up.
The figure will describe screening in Mega-ROX, identification of the final HIE cohort, first allocations, data-use exclusions, and primary-outcome availability. Purposeful receipt of the assigned strategy is reported among participants with permitted data use.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

Mega-ROX HIE denotes the nested trial; HIE denotes hypoxic ischemic encephalopathy. Final baseline diagnostic categories determine the principal cohort; original classifications are examined in the supporting sensitivities.

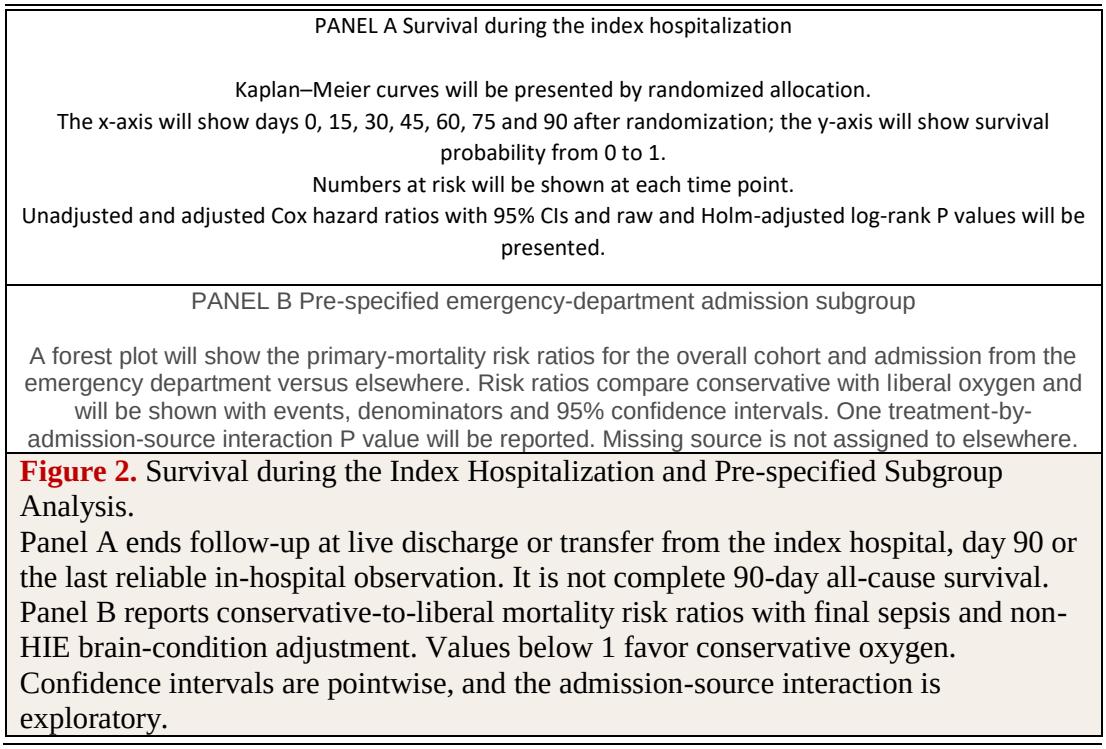


Figure 2. Survival during the Index Hospitalization and Pre-specified Subgroup Analysis.
Panel A ends follow-up at live discharge or transfer from the index hospital, day 90 or the last reliable in-hospital observation. It is not complete 90-day all-cause survival. Panel B reports conservative-to-liberal mortality risk ratios with final sepsis and non-HIE brain-condition adjustment. Values below 1 favor conservative oxygen. Confidence intervals are pointwise, and the admission-source interaction is 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. Conservative-to-liberal 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.

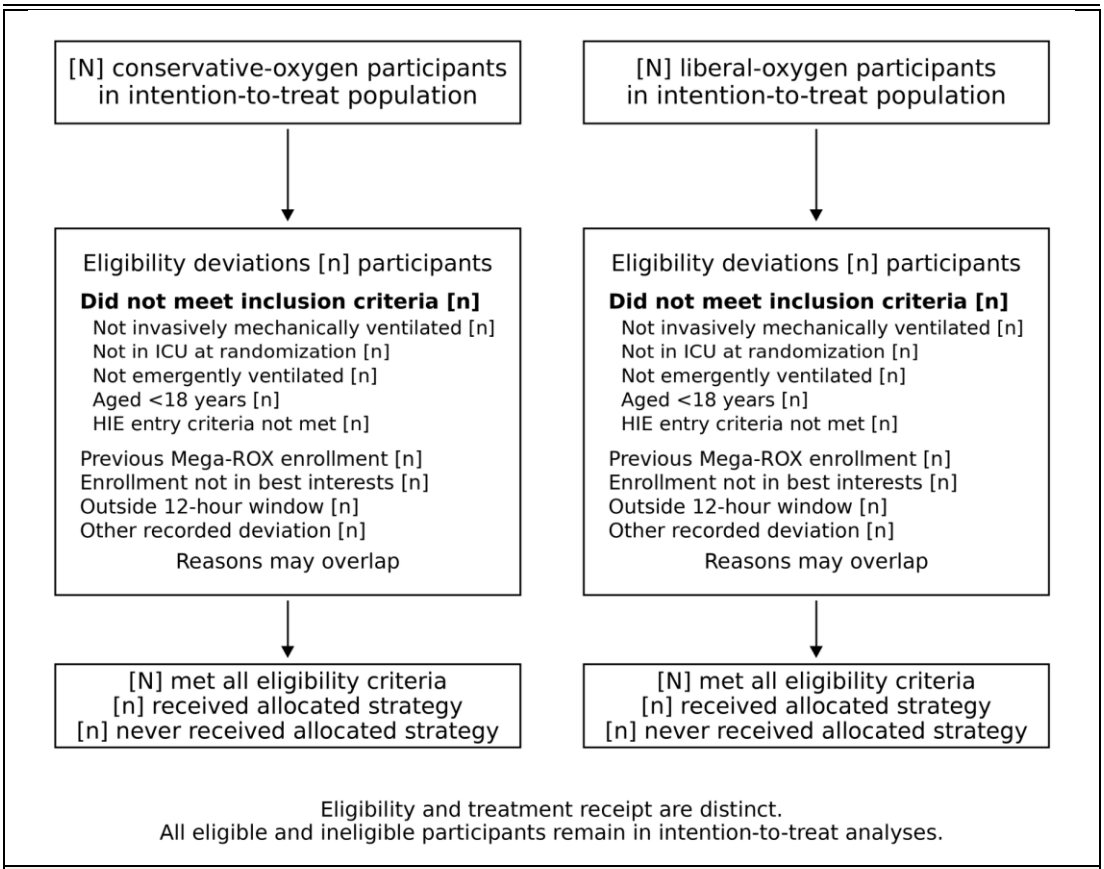


Figure 4. Protocol Deviations Affecting Trial Eligibility.
Participants and recorded reasons are summarized by randomized allocation. Reasons may overlap. Failure to receive treatment is classified separately from eligibility.

Mega-ROX HIE 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 5. 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 6. 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.

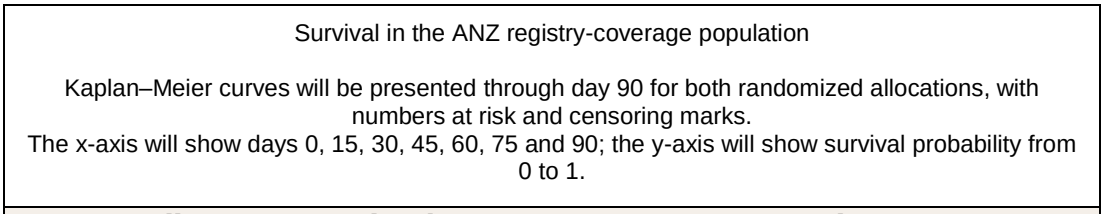


Figure 7. All-Cause Survival in the ANZ Registry-Coverage Population.
Deaths after index-hospital discharge will be included where registry coverage establishes follow-up. Follow-up will be censored at the last reliable all-cause observation or day 90. Reporting of this display is subject to the death registry linkage requirement in Section 27.