

Statistical Analysis Plan (SAP)

Trial: Conservative Oxygen for ICU Patients with Post-Cardiac-Arrest Brain Injury: the LOGICAL trial

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Section 1. Administrative Information

1. Title

Conservative Oxygen for ICU Patients with Post-Cardiac-Arrest Brain Injury: the LOGICAL trial

2. Trial registration

Prospectively registered (LOGICAL Australian and New Zealand Clinical Trials Registry number, ACTRN12621000518864)

3. SAP version

Version: 1.0 Date: 04/11/2025

4. Protocol Version

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

Young PJ. *et al.* Protocol summary and statistical analysis plan for the low oxygen intervention for cardiac arrest brain injury limitation (LOGICAL) trial. *Critical Care and Resuscitation* **25**, 140-146 (2023)¹.

5. SAP Revisions

This SAP provides additional details and clarifies analysis approaches outlined in the published version of the SAP. It supersedes analysis plans mentioned in the protocol.

6. Names and affiliations

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

Signatures:

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Date: 14/11/25

Section 2: Introduction

7. Brief background and rationale

Refer to the published protocol for a detailed background to this trial:

Young PJ. *et al.* Protocol summary and statistical analysis plan for the low oxygen intervention for cardiac arrest brain injury limitation (LOGICAL) trial. *Critical Care and Resuscitation* **25**, 140-146 (2023)¹.

8. Objectives

Research hypothesis:

We hypothesize that among adults in the ICU who are comatose with suspected hypoxic ischemic (HIE) following a cardiac arrest, conservative oxygen therapy, compared to liberal oxygen therapy, increases survival with a favorable neurological outcome measured with the Extended Glasgow Outcome Scale (GOS-E) at 180 from the date of randomization. A favorable neurological outcome is defined as a GOS-E score of lower moderate disability or better (i.e., a GOS-E score of 5-8).

Study objective:

To determine whether conservative oxygen therapy, compared to liberal oxygen therapy, increases favorable neurological outcome measured with the Extended Glasgow Outcome Scale (GOS-E) at 180 days from the date of randomization in patients who have suspected HIE following a cardiac arrest.

Section 3: Trial Methods

9. Trial design

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

10. Randomization

Treatment assignment was performed using a secure, centralized, web-based, randomization interface. Participants were enrolled in the study by ICU doctors, nurses, and research staff. The assigned intervention was communicated to the bedside nurse who implemented the study intervention. One novel feature of the Mega-ROX trials is that they use adaptive randomization to increase the probability that trial participants are allocated to the oxygen regimen that appears to be associated with the lowest in-hospital mortality risk based on available data from interim analyses. Randomization ratios of 1.05:1 in favor of liberal oxygen therapy, 1:1.05 in favor of conservative oxygen therapy, and 1:1 may all be used at different times of the trial. The method by which the randomization ratio that applied to a given patient in LOGICAL was determined as outlined in the protocol manuscript for the overarching Mega-ROX trial program. If at the time of Mega-ROX interim analyses the relative risk of mortality with conservative vs. liberal oxygen for patients with HIE is between 0.9 and 1.1, a randomization ratio of 1:1 will be applied until the next interim analysis. Otherwise, the randomization ratio will favor the oxygen regimen associated with the lowest risk of death.

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

11. Sample size

Allowing for loss to follow-up of 4%, a sample of 1400 patients provides 90% power to detect an 8.5% absolute difference between treatment groups in the proportion of patients who survive with a favorable neurological outcome at 180 days based on a control event rate of 32%. We increased the sample size to 1540 after the interim analysis to account for losses to follow-up and for protocol deviations involving enrollment of ineligible patients. After recruitment of 1181 patients, we further increased the sample size to 1840 because evaluation of aggregate baseline data revealed a higher than expected proportion of patients with asystole and pulseless electrical activity. We reasoned that such patients might be less likely to benefit from conservative oxygen therapy than patients with other presenting rhythms and so increased the sample size to account for this. Both increases in the sample size were supported by the Data Safety Monitoring Board.

12. Framework

This trial uses a superiority hypothesis testing framework between groups for the primary outcomes. Results will be reported in accordance with the CONSORT 2025 statement².

13. Statistical interim analyses and stopping guidance

We initially planned to conduct an interim analysis on the proportion of patients with a favorable neurological outcome measured with the GOS-E at 180 days post-randomization (the primary outcome) using data available at the time of recruitment of the 700th trial participant. However, because our recruitment rate was comparatively slow initially but then rose rapidly, this approach would have resulted in data being available for a relatively small number of participants. On the other hand, because recruitment rose rapidly, an alternative approach of waiting for the 700th patient to reach day 180 would have meant more than 1000 participants were recruited before the interim analysis occurred. Based on these considerations, on the advice of the Data Safety Monitoring Board, a single interim analysis using primary outcome data from the first 500 patients enrolled was conducted. This analysis used Haybittle Peto stopping criteria for benefit or harm with appropriate alpha spending (i.e. at the 0.001 level of significance) to preserve the overall alpha of 0.05. We did not apply stopping rules for futility.

We specified that if recruitment into either the overarching Mega-ROX trial or Mega-ROX HIE trial was halted at an interim analysis, the Data Safety Monitoring Board could suggest to the management committee that an additional interim analysis (or analyses) be conducted for the LOGICAL trial, or could recommend that the LOGICAL trial stop. Neither the overarching Mega-ROX trial nor Mega-ROX HIE trial stopped at an interim

analysis so additional interim analyses were not undertaken for the LOGICAL trial.

14. Timing of final analysis

The final analysis will be performed after all (n=1840) LOGICAL participants have reached the 180 day timepoint and been provided the opportunity to complete outcome measures and after the Statistical Analysis Plan has been finalized and published online. The Statistical Analysis Plan was finalized after analysis of a dataset with the final outcome data with randomly generated dummy randomized treatment group indicators.

15. Timing of outcome assessments

The primary outcome was planned to be collected at 180 days after randomization; actual timing of primary outcome data collection will be reported as median (interquartile range).

Section 4: Statistical Principles

16. Level of statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

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

No adjustment for multiplicity is planned.

18. Confidence intervals to be reported

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

19. Adherence and Protocol Deviations

The details of the oxygen therapy regimens that were used have been outlined in the protocol manuscript for the overarching Mega-ROX trial program. In brief, for patients allocated to conservative oxygen therapy, the lowest possible fraction of inspired oxygen (FiO_2) to achieve an arterial oxygen saturation on pulse oximetry (SpO_2) of $\geq 91\%$ was used. In this group, the protocol states that SpO_2 levels of greater than 94% were to be strictly avoided and an upper SpO_2 alarm limit of 95% was to be used whenever supplemental oxygen was being administered in the ICU to minimize the risk of exceeding the upper SpO_2 limit. For patients allocated to liberal oxygen therapy, oxygen was delivered as directed by the treating clinician with the caveat that the minimum FiO_2 allowed while the patient is invasively mechanically ventilated will be 0.30. The duration of study therapy was until ICU discharge or 90 days, whichever was sooner. The study interventions were applied in the ICU only. If patients were readmitted to ICU during their index hospital admission, they recommenced the study treatment to which they were randomized. If, during the course of their ICU admission, patients were transported outside of the ICU for procedures, they received standard (non-study) treatment. Similarly, if an increase in FiO_2 was required for procedures performed in the ICU including (but not limited to) bronchoscopy, suctioning, tracheostomy, or preparation for extubation, it was permitted in both groups. There were no restrictions to concomitant treatments provided to patients.

No analysis of outcomes excluding patients with minor deviations in the delivery of study treatment will be conducted. Such deviations will be transparently reported. These include patients in the conservative-oxygen group where FiO_2 was not reduced to 0.21 when the SpO_2 was 95%, and patients in the liberal-oxygen group where an FiO_2 less than 0.3 was used during mechanical ventilation.

Protocol deviations will be summarized by group as counts and percentages. Mean daily FiO_2 will be summarized by treatment group across days 0 to 7, as will highest FiO_2 daily and lowest FiO_2 daily. Mean daily arterial blood oxygen partial pressure (PaO_2) will be summarized by treatment group across days 0 to 7, as will highest PaO_2 daily and lowest PaO_2 daily.

For analyses that compare differences in the median percentage of hours per participant and the median number of hours per participant above and below specific SpO_2 thresholds (i.e., $<88\%$ and $>97\%$) and those that compare the median percentage of hours per participant and the median number of hours spent breathing an FiO_2 of 0.21 while in the ICU, we will calculate differences and medians and 95% CIs using quantile regression incorporating adjusting for site.

Analyses that compare the proportion of patients with at least one PaO_2 recording less than 60 mmHg and with at least one PaO_2 recording greater than 100 mmHg will be conducted via log-binomial models, adjusting for site. The numbers at risk in each group and the number and proportion of events observed will be reported, as well as the relative risk and corresponding 95% CIs.

20. Analysis Populations

Except where stated otherwise, all analyses will be conducted under the principle of intention-to-treat, whereby all participants are included in their randomized groups.

The primary outcome will also be analyzed for the following populations:

1. Eligible patients only. Some patients who were not eligible for the study were inadvertently randomized; an analysis of the primary outcome excluding these ineligible patients will be conducted.
2. Eligible patients who received their randomized treatment only. In addition to excluding ineligible patients, eligible patients who never received their randomized treatment will be excluded in this analysis.

Section 5: Trial Population

21. Screening Data

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

22. Eligibility

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

23. Recruitment

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

24. Withdrawal/follow-up

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

25. Baseline descriptive measures

See Appendix for all planned tables.

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

An appendix table will provide summaries of baseline characteristics and compare these characteristics between two groups: those patients for whom the primary outcome at 180 days was provided, and those patients for whom the primary outcome is missing. T-tests will be used to compare continuous characteristics between these groups, and chi-squared tests will be used to compare categorical characteristics, and this will help to determine which variables should be included as auxiliary variables in models for the imputation of the outcome.

Section 6: Analysis

26. Outcome definitions

Name	Description	Scale	Outcome definition
Primary Outcome			
Unfavorable functional outcome at day 180	Dichotomization of GOS-E score	Binary variable: 0 = Favorable GOS-E (GOS-E score 5-8) 1= Unfavorable GOS-E (GOS-E score 1-4)	GOS-E score at day 180. GOS-E: Extended Glasgow Outcome Scale For the primary analysis, patients who died after day 180 but before their outcome assessment will have GOS-E set to 1.
Secondary Outcomes			
Day 180 mortality	Mortality up to day 180 after randomization	Binary variable: 0 = alive at day 180; 1 = dead at day 180	Binary mortality variable.
Quality of Life	EQ-5D-5L utility, with subscales combined using Australian 2023 tariff	Scores range from -0.3 to 1	Quality of life at day 180 with value of 0 imputed for patients who die prior to day 180 (this corresponds to the hypothetical strategy for dealing with the intercurrent event of death).
MOCA-Blind	MoCA-Blind assesses cognition in domains of attention, memory, language, abstraction, and orientation.	The maximum score is 22, with higher scores indicating better cognitive performance; a score of 18 or greater is typically considered normal.	MOCA-Blind at day 180 with value of 0 imputed for patients who die prior to day 180 (this corresponds to the hypothetical strategy for dealing with the intercurrent event of death).
Patient / proxy reported health state scale	EQ visual analogue scale	Ranges from 0 to 100 where 0 is described as “the worst health state you can imagine” and 100 described is “the best health state you can imagine	EQ visual analogue scale (EQ VAS) at day 180 with value of 0 imputed for patients who die prior to day 180 (this corresponds to the hypothetical strategy for dealing with the intercurrent event of death).
Hours of invasive mechanical ventilation	Number of days to liberation from ventilation	Censored time-to-event variable, measured in parts of full days with a competing risk of death	Number of days after commencement of mechanical ventilation to liberation from invasive mechanical ventilation or death
Days in ICU	Number of days to discharge from ICU	Censored time-to-event variable, measured in parts of full days with a competing risk of death	Number of days after admission to ICU to discharge from ICU or death. If discharge time missing, assumed to be at midday.

Days in hospital	Number of days to discharge from hospital	Censored time-to-event variable, measured in parts of full days with a competing risk of death	Number of days after admission to hospital to discharge from hospital or death. If discharge time missing, assumed to be at midday.
Survived and discharged directly home from hospital	Was a patient discharged alive to home	Binary variable: 0 = died in hospital or not discharged home; 1 = alive and discharged directly home	Outcome recorded at time of in-hospital mortality or at hospital discharge
Time to death	Time at which mortality outcome recorded	Censored time-to-event variable, measured in parts of full days.	Number of days after randomization to death

27. Analysis methods

Analysis of primary outcome and binary secondary outcomes:

For the primary analysis of binary outcomes we will use log-binomial models adjusting for the presence of non-HIE brain injuries and conditions, and sepsis at baseline. These characteristics are to be included in the model because patients with these diagnoses were also included in the Mega-ROX Brains and Mega-ROX Sepsis studies respectively, so there is potential for imbalance in these characteristics across arms of LOGICAL. Adjustment for site as a random effect will also be incorporated in the primary analysis. The number and proportion of events observed will be reported, as well as the equivalent absolute risk difference and relative risk ratio and corresponding 95% confidence intervals: the risk difference will be obtained from a model with an identity link function; the relative risk obtained from a model with a log link function. To enable alignment in effect direction between mortality and GOS-E, data will be presented showing the proportion of patients with an unfavorable outcome rather than a favorable one.

If models fail to converge:

For complete case analyses:

1. For outcomes analyzed via a log-binomial model with adjustment for site as a random effect, if the model fails to converge (including terms for presence of non-HIE acute brain injuries and conditions and sepsis at baseline), the following steps will be taken, with estimates from the first of these that converges presented:
 - a. Fit a log-binomial with the same link function, adjusting for site with cluster-robust standard errors instead of random effects for site
 - b. Combine sites with fewer than 10 patients together and fit the original model.
 - c. Combine sites with fewer than 20 patients together and fit the original model.
 - d. Fit the log-binomial model with adjustment for site as a random effect, including a term for sepsis at baseline only
 - e. Fit the log-binomial model with adjustment for site as a random effect, including a term for presence of non-HIE acute brain injuries and conditions
 - f. Fit the log-binomial model with adjustment for site as a random effect without including any additional covariates.

For analyses based on multiply imputed datasets: if a model fails to converge for more than one quarter of imputed datasets, steps as above for complete-case analyses will be taken, with a method deemed “successful” and results presented if it converges for at least 75% of imputed datasets.

Time-to-event outcomes

Time to death will be analyzed by fitting a Cox proportional hazards model, including terms for presence of non-HIE acute brain injuries and conditions and sepsis at baseline, with robust

standard errors to account for clustering by site. If estimation fails, small sites (fewer than 10 patients initially and then fewer than 20, if necessary) will be combined and the model re-fit. A Kaplan-Meier plot survival plot will be presented.

To account for the competing risk of death, duration of invasive mechanical ventilation, ICU and hospital lengths of stay will be analyzed using sub distribution hazard regression models, including terms for presence of non-HIE acute brain injuries and conditions and sepsis at baseline, with robust standard errors to account for clustering by site. If estimation fails, small sites (fewer than 10 patients initially and then fewer than 20, if necessary) will be combined and the model re-fit. Cumulative incidence functions will also be presented (code provided below).

Median times to extubation, discharge from ICU and discharge from hospital will be compared between groups using quantile regression including terms for presence of non-HIE acute brain injuries and conditions and sepsis at baseline with adjustment for site.

The distributions of the logarithm of each of time to extubation, time to discharge from ICU and time to discharge from hospital have approximately normal distributions. Geometric means will be reported for logarithms of each of these outcomes (by treatment group, and by treatment group and by survival to the event of interest – extubation, ICU discharge, or hospital discharge). Differences between the geometric means of randomized groups will be reported as a ratio, obtained from linear regression models, including terms for presence of non-HIE acute brain injuries and conditions and sepsis at baseline, with robust standard errors to account for clustering by site.

Skewed continuous outcomes

In the SAP it was stated that scores on the EQ 5D-5L and the MoCA-Blind at day 180 were to be evaluated using quantile regression with adjustment for site. However, given the large proportion of deaths observed in the dataset with dummy treatment codes, this is unlikely to be appropriate. To analyze these outcomes, aligned rank-sum (Hodges-Lehmann) tests will be applied.

In addition, survivor average causal effects will be estimated for these outcomes. That is, the effect of the treatment group in the hypothetical stratum of patients who would survive to 180 days will be estimated. The method of Tchetgen Tchetgen et al³ will be applied. The probability of survival will be estimated using a logistic regression model including terms for treatment, presence of non-HIE acute brain injuries and conditions and sepsis at baseline, patient age, and arrest location, and a term for probability of non-survival included in the quantile regression model for the outcome, with adjustment for site. The 95% confidence interval for the difference in medians between groups will be obtained using non-parametric bootstrap, with at least 1000 bootstrapped samples.

EQ VAS will be analyzed in the same way as EQ 5D-5L and the MoCA-Blind at day 180.

28. Statistical Methods – adjustment for covariates

For the analysis of the primary outcome including age, cardiac arrest location outside of hospital, shockable first monitored rhythm, time to return of spontaneous circulation, whether there was a medical cause for arrest, whether the patient had an ST elevation acute myocardial infarction, and baseline variables that were imbalanced, should the models fail to converge, the same steps as above will be taken, with removal of covariates one-at-a-time in this order from least important to most important:

- a. baseline variables that were imbalanced; whether the patient had an ST elevation acute MI; whether there was a medical cause for arrest; cardiac arrest location outside of hospital; age; shockable first monitored rhythm; time to return of spontaneous circulation.
- b. Should all of those models fail to converge, pairs of covariates will be removed until the

model converges, using the order specified above to define pairs (e.g. (#1, #2), (#1, #3), ..., (#k-1, #k))

29. Statistical Methods – sensitivity analyses

For those patients who died after day 180 but before their day 180 assessment, GOS-E outcomes will be imputed using the multiple imputation method as described below.

The primary outcome will be analyzed as an ordinal variable via ordered logistic regression, including terms for randomized group, presence of non-HIE acute brain injuries and conditions and sepsis at baseline, with robust standard errors accounting for site. The Brant test will be applied to assess proportionality assumptions. If the hypothesis of proportionality is rejected, then an aligned rank-sum (Hodges-Lehmann) test will be applied.

30. Statistical Methods – subgroup analyses

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

- i) Out-of-hospital vs in-hospital cardiac arrest;
- ii) First monitored rhythm shockable vs first monitored rhythm not shockable;
- iii) Medical cause of cardiac arrest vs other cause of cardiac arrest.

Models for these analyses will be as described in Section 27 for the primary outcome, including terms for the subgroup indicator and interactions between the subgroup and randomised group. Treatment effects in each subgroup will be reported.

31. Missing data reporting and assumptions/statistical methods to handle missing data

Multiple imputation of outcomes was undertaken with the analysis of multiply imputed data designation as the primary analysis. In analysis of data with randomly generated dummy treatment codes, 114/1821(6.3%) of patients had missing primary outcome data, so multiple imputation will be conducted, with 20 datasets imputed. Participants who did not provide consent for collection of outcomes at day 180, but did provide consent for use of baseline data, will be included in the intention to treat population and had their outcomes imputed.

Missing baseline characteristics will be imputed using single mean imputation, using centre-specific means. Baseline characteristics of participants who did and did not provide the primary outcome were compared, and were used to inform multiple imputation models. T-tests or Wilcoxon rank-sum tests were used to compare continuous characteristics (depending on whether these had approximately symmetric distributions or not); chi-squared tests compared categorical characteristics between participants with and without the primary outcome.

Missing outcome values will be imputed separately by treatment group. Imputation models will include baseline characteristics that appear to be different between participants who provided complete follow up data and participants who did not. Based on analysis of data with dummy treatment codes, imputation models will include age, fraction of inspired oxygen prior to randomization, arrest location and cause of arrest. These are complete and appear to be associated with observation of the primary outcome. Imputation models for continuous outcomes will also include terms for site. Imputation models for binary outcomes will not include terms for site due to the possibility of perfect prediction in small sites.

The GOSE score will be imputed using linear regression with predictive mean matching from the 5 nearest neighbours. The primary outcome (unfavorable functional outcome) will then be derived from the imputed GOSE score. Imputation for MOCA-Blind and quality of life will be chained together with predictive mean matching from the 5 nearest neighbours, with data only from patients who are not known to have died prior to day 180 included in prediction models. Times to extubation, discharge from ICU and discharge from hospital will be chained

together with predictive mean matching from the 5 nearest neighbours. Death up to 180 days post randomization and discharge home outcomes will be imputed separately using logistic regression models. Terms for location of arrest and/or cause of arrest may need to be excluded from imputation models in the case of perfect prediction of outcomes.

Imputed datasets will be compared to complete data using density plots for continuous outcomes and plots of proportions for binary outcomes.

32. Harms

Adverse events will be reported by treatment group.

33. Statistical Software and code

Stata v19 or later will be used (StataCorp. Stata Statistical Software: Release 19. College Station, TX: StataCorp LLC); or R v 4.4.1 or later. Any user-written R packages used will be referenced.

The following code will be applied for the analysis of primary and secondary outcomes:
Primary outcome and binary secondary outcomes:

```
xi: gllamm outcome i.TreatmentGroup Sepsis NonHIEABI,  
i(LOG_D180Site_num) fam(binomial) link(log)
```

Time to death outcome

```
stset timetodeath, failure(Died_180)  
  
stcox i.TreatmentGroup Sepsis NonHIEABI, vce(cluster  
LOG_D180Site_num)
```

Time-to-event outcomes with competing risk of death

```
stset outcome, failure(outc==1)  
  
stcrreg i.TreatmentGroup Sepsis NonHIEABI, compete(outc==2)  
vce(cluster LOG_D180Site_num)
```

R code for the generation of cumulative incidence curves (using the `tidycmprsk`, `ggsurvfit`, `magrittr` packages):

```
cuminc(Surv(Timetoevent, Event) ~ TreatmentGroup, DataSet,  
strata=DataSet$LOG_D180Site_num) %>%  
  ggcuminc(outcome = c(1,2)) +  
  add_confidence_interval() +  
  add_risktable() +  
  scale_ggsurvfit()
```

34. Modifications from published SAP

1. Details of and the rationale for increasing sample size have been provided.
2. Details of and reasons for the revised interim analysis schedule have been provided.
3. A complete set of shell tables and figures has been specified. Several tables and figures were not present in the published SAP: LIST OF NEW TABLES AND FIGURES
4. That p-values will not be adjusted due to multiple hypothesis testing has been clarified.

5. That patients with minor deviations in the analysis of study treatment will not be excluded from the analysis of outcomes has been stated.
6. We had indicated that repeated measures of oxygen exposure metrics on each participant (PaO₂ and FiO₂) would be evaluated by fitting mixed linear models, including main effects for treatment and time and an interaction between the two to determine if treatments differed over time, with random intercepts for site and for individual. However, as we do not intend reporting P values (except for the primary outcome) we have determined that oxygen exposure will be adequately described using other metrics.
7. Time from ROSC until randomization included in baseline characteristics table.
8. That the primary outcome (unfavorable functional outcome at day 180) will be set to 1 for those patients who died after day 180 but before outcome assessment occurred for the primary analysis was clarified.
9. That the EQ VAS will also be analyzed (using the same method as EQ 5D-5L and the MoCA-Blind at day 180) has been stated.
10. That the quality of life outcome (EQ5D5L) will be analyzed as the combination of the EQ5D5L subscales using the Australian 2023 tariff has been clarified.
11. That the analysis population would consist of all randomized patients (including those who were ineligible, provided there is consent) was clarified. Two additional analysis populations for the primary outcome were described: eligible patients only, and eligible patients who received their randomized treatment only.
12. That risk differences would be obtained from log-binomial models with an identity link function and relative risks obtained from log-binomial models with a log link function has been clarified. In the SAP “multivariate logistic models” for the primary outcome were mentioned when discussing the independent covariates to be included in Cox proportional hazards model for time to death; we note that only log-binomial models (with identity and log links) will be fit for the primary outcome.
13. Alternative analysis approaches should models fail to converge were have been specified, along with sample code for the primary analysis method.
14. In the SAP the pre-specified analysis of the MOCA-Blind and quality of life outcomes was quantile regression with adjustment for site. However, given that in the analysis of the data set with dummy codes for treatment >50% of patients had died by day 180, this analysis is not likely to be appropriate. Instead the aligned rank-sum (Hodges-Lehmann) test will be applied, as well as estimation of survivor average causal effects.
15. That the time to death outcome will be analyzed via a Cox proportional hazards model including terms for presence of non-HIE acute brain injuries and conditions and sepsis at baseline has been specified.
16. That cumulative incidence functions will also be presented for duration of mechanical ventilation, ICU and hospital lengths of stay has been included, with code for these figures included. Differences in medians will also be calculated using quantile regression.
17. That duration of invasive mechanical ventilation will be analyzed as ICU and hospital lengths of stay has been clarified.
18. That the Brant test will be applied to assess proportionality assumptions has been stated.
19. Additional detail on the approach to multiple imputation has been provided, based on analysis of data with dummy codes.

35. References

1. Young PJ, Hodgson CL, Mackle D, et al. Protocol summary and statistical analysis plan for the low oxygen intervention for cardiac arrest injury limitation (LOGICAL) trial. *Crit Care Resusc* 2023;25(3):140-146. DOI: 10.1016/j.ccrj.2023.06.007.
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 5. Wittich W, Phillips N, Nasreddine ZS, Chertkow H. Sensitivity and Specificity of the Montreal Cognitive Assessment Modified for Individuals who are Visually Impaired. Journal of Visual Impairment & Blindness 2010;104(6):360-368. DOI: 10.1177/0145482x1010400606.

36. Appendix: Planned tables and figures

Table 1: Characteristics of Patients at Baseline*		
Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Comorbid conditions – no. (%)		
Hypertension	xxx (xx.x)	xxx (xx.x)
Diabetes	xxx (xx.x)	xxx (xx.x)
Ischemic heart disease	xxx (xx.x)	xxx (xx.x)
Asthma or COPD	xxx (xx.x)	xxx (xx.x)
Previous myocardial infarction	xxx (xx.x)	xxx (xx.x)
Previous cardiac arrhythmia	xxx (xx.x)	xxx (xx.x)
Percutaneous coronary intervention	xxx (xx.x)	xxx (xx.x)
Congestive heart failure	xxx (xx.x)	xxx (xx.x)
Previous CABG	xxx (xx.x)	xxx (xx.x)
Previous TIA or stroke	xxx (xx.x)	xxx (xx.x)
Cardiac arrest location – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
ICU	xxx (xx.x)	xxx (xx.x)
Operating theatre	xxx (xx.x)	xxx (xx.x)
Other location in hospital	xxx (xx.x)	xxx (xx.x)
Home / residence	xxx (xx.x)	xxx (xx.x)
Assisted living / nursing home	xxx (xx.x)	xxx (xx.x)
Other location (not in hospital)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)
Witnessed cardiac arrest† – no. (%)	xxx (xx.x)	xxx (xx.x)
Bystander CPR – no. (%)	xxx (xx.x)	xxx (xx.x)
First monitored rhythm VF, VT, or AED shockable – no. (%)	xxx (xx.x)	xxx (xx.x)
Response time – mins	xx.x ± xx	xx.x ± xx
Time to defibrillation – mins	xx.x ± xx	xx.x ± xx
Time until sustained ROSC – mins	xx.x ± xx	xx.x ± xx
Cause of cardiac arrest – no. (%)		
Medical	xxx (xx.x)	xxx (xx.x)
Asphyxia	xxx (xx.x)	xxx (xx.x)
Drug overdose	xxx (xx.x)	xxx (xx.x)
Drowning	xxx (xx.x)	xxx (xx.x)
Electrocution	xxx (xx.x)	xxx (xx.x)
Traumatic	xxx (xx.x)	xxx (xx.x)
Unknown / not reported	xxx (xx.x)	xxx (xx.x)
Presence of STEMI – no. (%)	xxx (xx.x)	xxx (xx.x)
Median PaO ₂ (IQR) – mmHg	xx (xx to xx)	xx (xx to xx)
FIO ₂	x.xx ± xx	x.xx ± xx
Median time from ROSC to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are expressed as mean ± SD.

† A witnessed arrest was defined as one that was seen or heard by another person or was monitored.

Abbreviations: AED: automated external defibrillator; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; FIO₂: fraction of inspired oxygen; ICU: intensive care unit; IQR: interquartile range; OR: operating room; PaCO₂: arterial partial pressure of carbon dioxide; PaO₂: arterial partial pressure of oxygen; PEEP: positive end expiratory pressure; ROSC: return of spontaneous circulation; SD: standard deviation; SpO₂: arterial oxygen saturation on pulse oximetry; STEMI: ST elevation acute myocardial infarction TIA: transient ischemic attack; VF: ventricular fibrillation; VT: ventricular tachycardia.

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

* The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† All differences in median values were calculated with the use of quantile regression after adjustment for trial site.

‡ Relative risks were calculated using log-binomial models, adjusting for trial site.

Abbreviations: CI denotes confidence interval, IQR interquartile range, FIO₂ fraction of inspired oxygen, and SpO₂ arterial oxygen saturation as measured by pulse oximetry.

Table 3: Primary and Secondary Outcomes*				
	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)	Between-Group Difference†	Relative risk‡ (95% CI)
Primary outcome				
Unfavorable functional outcome at day 180§, n (%)	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Secondary outcomes				
Day 180 mortality , n (%)	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median quality of life EQ utility score¶ (IQR)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)	
Survivors only	xx (xx to xx)	xx (xx to xx)		
Median patient / proxy reported health state scale** (IQR)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)	
Survivors only	xx (xx to xx)	xx (xx to xx)		
Median MoCA-Blind†† (IQR)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)	
Survivors only	xx (xx to xx)	xx (xx to xx)		
Median hours of invasive mechanical ventilation (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median days in ICU (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median days in hospital (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Survived and were discharged directly home from hospital, n (%)	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* The widths of the confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups. Missing outcome values for the intention to treat population (see Figure 1) were imputed using chained equations and predictive mean matching using the five nearest neighbors (details of imputation methods are provided in the Supplementary Appendix).

† The between-group difference in the primary outcome and the difference in percentage of patients discharged home were calculated using binomial regression with an identity link. The between group differences in median hours of mechanical ventilation, days in ICU and days in hospital were calculated using quantile regression adjusting for site.

‡ Relative risks were calculated using log-binomial models adjusting for the presence of non-ischemic encephalopathy brain injuries and conditions, and sepsis at baseline incorporating adjustment of site as a random effect.

§ The primary outcome was favorable neurological outcome measured with the Extended Glasgow Outcome Scale (GOS-E) at 180 days post randomization. To enable alignment in effect direction between mortality and GOS-E, data are presented showing the proportion of patients with an unfavorable outcome rather than a favorable one.

|| Survival data are shown in Figure 2 and cause-specific mortality data are provided in Table S9 in the Supplementary Appendix.

¶ Quality of life was assessed using the EQ-5D-5L; this scale evaluates mobility, self-care, usual activities, pain or discomfort, and anxiety and depression, with categorization of each of these dimensions into five levels that range from no problems to extreme problems. The EQ-5D-5L was converted to an EQ utility score, which ranges from -0.6 to 1.0, with 1.0 indicating the best health state. Patients who died were assigned a score of zero. For transparency, data for patients who survived are presented separately.

** The patient's health state was rated using the EQ visual analogue scale which ranges from 0 to 100 where 0 is described as "the worst health state you can imagine" and 100 described is "the best health state you can imagine. Patients who died were assigned a score of zero. For transparency, data for patients who survived are presented separately.

†† The MoCA-Blind assesses cognition in domains of attention, memory, language, abstraction, and orientation. The maximum score is 22, with higher scores indicating better cognitive performance; a score of 18 or greater is typically considered normal. An extra point was added for patients who scored less than 22 and who had 12 years or less of formal education. Patients who died were assigned a score of zero. For transparency, data for patients who survived are presented separately.

Abbreviations: CI: confidence interval; IQR: interquartile range; GOS-E: Extended Glasgow Outcome Scale; MoCA-Blind: Montreal Cognitive Assessment-Blind.

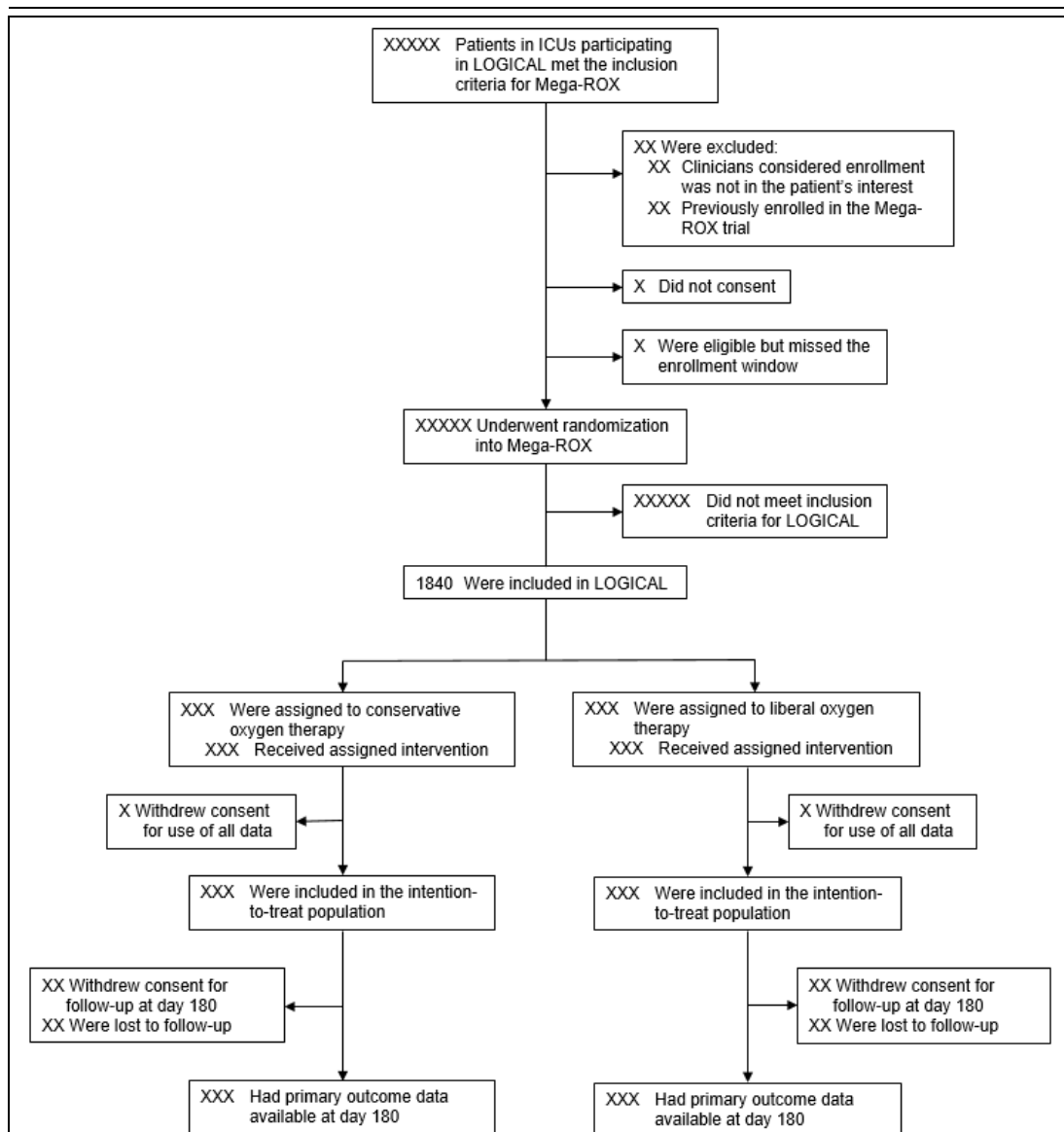


Figure 1. Randomization and Follow-up.

The exclusion for enrollment not being in the patient's interests included situations where death was deemed imminent and inevitable.

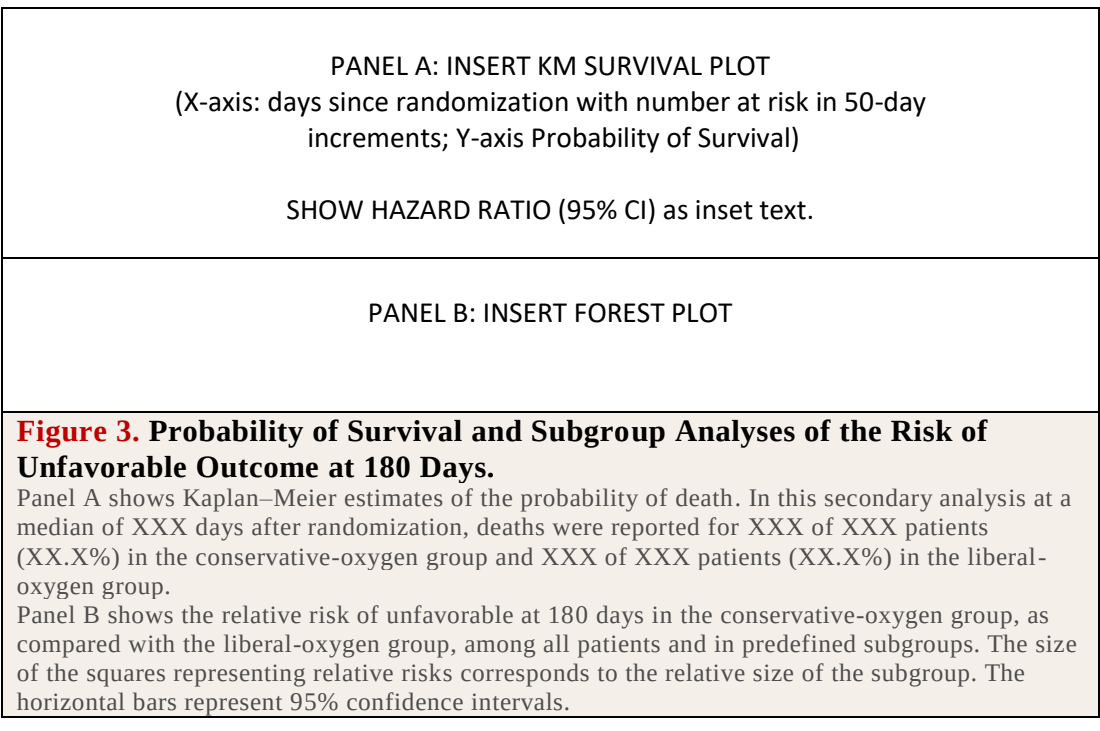
Abbreviations: ICU: intensive care unit; LOGICAL: Low Oxygenation Goals in Cardiac Arrest injury Limitation; Mega-ROX: Mega Randomized Registry Trial Research Program

STACKED BAR CHART FOR GOS-E CATEGORIES AT 180 DAYS FOR
CONSERVATIVE-OXYGEN GROUP AND LIBERAL-OXYGEN GROUP

**Figure 2. Stacked Bar Chart of Extended Glasgow Outcome Scale (GOS-E)
Results at Day 180.**

Levels on the GOS-E range from 1 (death) to 8 (“upper good recovery” [no injury-related problems]). For the primary analysis, categories were dichotomized into “death or survival with an unfavorable functional outcome” (which included “death,” “vegetative state,” “lower severe disability,” and “upper severe disability” [GOS-E levels of 1 to 4]) and “survival with a favorable functional outcome” (which included “lower moderate disability,” “upper moderate disability,” “lower good recovery,” and “upper good recovery” [GOS-E levels of 5 to 8]). An unfavorable functional outcome (a GOS-E level of 1 to 4) was observed for XX of XX patients (XX.X%) in the conservative-oxygen group and XX of XX patients (XX.X%) in the liberal-oxygen group (absolute risk difference, X.X percentage points; 95% CI, X.X to X.X; adjusted risk ratio, X.XX; 95% CI, X.XX to X.XX; P=X.XX).

Abbreviations: CI: confidence interval; GOS-E: Extended Glasgow Outcome Scale.



37. Supplementary tables

Numbering of Tables reflects anticipated numbering in the manuscript (Tables S1 and S2 are not shown below because these tables will contain methods)

Table S3: Ethnicity data for Australian and New Zealand trial participants		
Characteristic	Conservative oxygen	Liberal oxygen
New Zealand participants	n=xxx	n=xxx
Ethnicity – n (%)		
New Zealand European	xxx (xx.x)	xxx (xx.x)
Māori	xxx (xx.x)	xxx (xx.x)
Pacific peoples	xxx (xx.x)	xxx (xx.x)
Asian	xxx (xx.x)	xxx (xx.x)
Middle Eastern, Latin American, and African	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)
Australian participants	n=xxx	n=xxx
Ethnicity – n (%)		
Indigenous Australian	xxx (xx.x)	xxx (xx.x)
Not indigenous Australian	xxx (xx.x)	xxx (xx.x)

Table S4: Characteristics of the Patients with and without the Primary Outcome Available*

Characteristic	Primary outcome available (n=XXX)	Primary outcome not available (n=XXX)
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Comorbid conditions – no. (%)		
Hypertension	xxx (xx.x)	xxx (xx.x)
Diabetes	xxx (xx.x)	xxx (xx.x)
Ischemic heart disease	xxx (xx.x)	xxx (xx.x)
Asthma or COPD	xxx (xx.x)	xxx (xx.x)
Previous myocardial infarction	xxx (xx.x)	xxx (xx.x)
Previous cardiac arrhythmia	xxx (xx.x)	xxx (xx.x)
Percutaneous coronary intervention	xxx (xx.x)	xxx (xx.x)
Congestive heart failure	xxx (xx.x)	xxx (xx.x)
Previous CABG	xxx (xx.x)	xxx (xx.x)
Previous TIA or stroke	xxx (xx.x)	xxx (xx.x)
Cardiac arrest location – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
ICU	xxx (xx.x)	xxx (xx.x)
Operating theatre	xxx (xx.x)	xxx (xx.x)
Other location in hospital	xxx (xx.x)	xxx (xx.x)
Home / residence	xxx (xx.x)	xxx (xx.x)
Assisted living / nursing home	xxx (xx.x)	xxx (xx.x)
Other location (not in hospital)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)
Witnessed cardiac arrest† – no. (%)	xxx (xx.x)	xxx (xx.x)
Bystander CPR – no. (%)	xxx (xx.x)	xxx (xx.x)
First monitored rhythm VF, VT, or AED shockable – no. (%)	xxx (xx.x)	xxx (xx.x)
Response time – mins	xx.x ± xx	xx.x ± xx
Time to defibrillation – mins	xx.x ± xx	xx.x ± xx
Time until sustained ROSC – mins	xx.x ± xx	xx.x ± xx
Cause of cardiac arrest – no. (%)		
Medical	xxx (xx.x)	xxx (xx.x)
Asphyxia	xxx (xx.x)	xxx (xx.x)
Drug overdose	xxx (xx.x)	xxx (xx.x)
Drowning	xxx (xx.x)	xxx (xx.x)
Electrocution	xxx (xx.x)	xxx (xx.x)
Traumatic	xxx (xx.x)	xxx (xx.x)
Unknown / not reported	xxx (xx.x)	xxx (xx.x)
Presence of STEMI – no. (%)	xxx (xx.x)	xxx (xx.x)
Median PaO ₂ (IQR) – mmHg	xx (xx to xx)	xx (xx to xx)
FIO ₂	x.xx ± xx	x.xx ± xx
Median time from ROSC to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are expressed as mean ± SD.

† A witnessed arrest was defined as one that was seen or heard by another person or was monitored.

Abbreviations: AED: automated external defibrillator; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; FIO₂: fraction of inspired oxygen; ICU: Intensive Care Unit; IQR: interquartile range; OR: operating room; PaCO₂: arterial partial pressure of carbon dioxide; PaO₂: arterial partial pressure of oxygen; PEEP: positive end expiratory pressure; ROSC: return of spontaneous circulation; SD: standard deviation; SpO₂: arterial oxygen saturation on pulse oximetry; STEMI: ST elevation acute myocardial infarction TIA: transient ischemic attack; VF: ventricular fibrillation; VT: ventricular tachycardia.

Table S5: Representativeness of the trial participants*		
Characteristic	ANZ trial patients (n=xxxx)	Overall ANZ ICU cardiac arrest population (n=xxxx)
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
APACHE-II co-morbidities – n (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Hepatic	xxx (xx.x)	xxx (xx.x)
Kidney	xxx (xx.x)	xxx (xx.x)
Immunosuppression	xxx (xx.x)	xxx (xx.x)
Metastatic cancer	xxx (xx.x)	xxx (xx.x)
Source of admission to ICU – n (%)	xxx (xx.x)	xxx (xx.x)
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following elective surgery	xxx (xx.x)	xxx (xx.x)
From OT following emergency surgery	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)
APACHE-II score	xx.x ± xx	xx.x ± xx

Plus-minus values are expressed as mean ± SD.

* Participating ICUs (Australia – 40 ICUs, Ireland – 1 ICU, and New Zealand 12 ICUs) were in high income countries. To evaluate representativeness, we report the characteristics of enrolled patients from Australian and New Zealand to those of all adults who had a cardiac arrest prior to ICU admission who were invasively mechanically ventilated on the day of admission to an Australian or New Zealand ICU (except those admitted to ICU for palliative care or organ donation). Data were obtained from the Australian and New Zealand Intensive Care Centre for Outcome and Resource Evaluation Adult Patient Database. Data from the three patients enrolled in Ireland were not included in this Table.

† Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

Abbreviations: ANZ: Australia and New Zealand; APACHE: Acute Physiology And Chronic Health Evaluation; ICU: intensive care unit; OT: operating theatre

Table S6: Situations where allocated treatment was not received or was not delivered in accordance with the study protocol		
Nature of deviation	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Allocated treatment never given – n (%)	xxx (xx.x)	xxx (xx.x)
Ineligible patient: Enrolled and immediately withdrawn as treatment considered not to be in the patient's best interests	xxx (xx.x)	xxx (xx.x)
Ineligible patient: Enrolled prior to ICU admission (in error); died before reaching the ICU	xxx (xx.x)	xxx (xx.x)
On ECMO for the entire ICU stay	xxx (xx.x)	xxx (xx.x)
Received allocated treatment but one or more deviations were recorded		
FiO ₂ greater than 0.21 and not reduced when the SpO ₂ was 95% or more	xxx (xx.x)	Not applicable
Used an FiO ₂ less 0.3 during mechanical ventilation	Not applicable	xxx (xx.x)

Abbreviations: ECMO: extracorporeal membrane oxygenation; FiO₂: fraction of inspired oxygen; ICU: intensive care unit; PaO₂: arterial partial pressure of oxygen. SaO₂: arterial oxygen saturation. SpO₂: arterial oxygen saturation measured by peripheral pulse oximetry.

Table S7: Treatment and neuroprognostication tests used in trial participants		
Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Drugs given during resuscitation – n (%)		
Adrenaline	xxx (xx.x)	xxx (xx.x)
Amiodarone	xxx (xx.x)	xxx (xx.x)
Vasopressin	xxx (xx.x)	xxx (xx.x)
No adrenaline, amiodarone, or vasopressin given	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)
Temperature management*		
Targeted temperature management used, n (%)		
Yes	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)
Lowest temperature on day 0 in ICU	xx.x ± x.x	xx.x ± x.x
Highest temperature on day 0 in ICU	xx.x ± x.x	xx.x ± x.x
Lowest temperature on day 1 in ICU	xx.x ± x.x	xx.x ± x.x
Highest temperature on day 1 in ICU	xx.x ± x.x	xx.x ± x.x
Lowest temperature on day 2 in ICU	xx.x ± x.x	xx.x ± x.x
Highest temperature on day 2 in ICU	xx.x ± x.x	xx.x ± x.x
Neuroprognostic tests performed – n (%)		
Somatosensory evoked potentials	xxx (xx.x)	xxx (xx.x)
Neurone specific enolase	xxx (xx.x)	xxx (xx.x)
Electroencephalogram	xxx (xx.x)	xxx (xx.x)
CT brain	xxx (xx.x)	xxx (xx.x)
MRI brain	xxx (xx.x)	xxx (xx.x)

* Day 0 is the day of randomization.

Abbreviations: CT: computed tomography; ICU: intensive care unit; MRI: magnetic resonance imaging

Table S8: Complete Case Analysis of Primary and Secondary Outcomes*				
	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)	Between-Group Difference†	Relative risk‡ (95% CI)
Primary outcome				
Unfavorable functional outcome at day 180§, n (%)	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Secondary outcomes				
Day 180 mortality , n (%)	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median quality of life EQ utility score¶ (IQR)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)	
Median MoCA-Blind** (IQR)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)	
Median hours of invasive mechanical ventilation (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median days in ICU (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median days in hospital (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Survived and were discharged directly home from hospital, n (%)	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* The widths of the confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† The between-group difference in the primary outcome and the difference in percentage of patients discharged home was calculated using binomial regression with an identity link. The between group differences in median hours of mechanical ventilation, median days in ICU and median days in hospital were calculated using quantile regression adjusting for site.

‡ Relative risks were calculated using log-binomial models adjusting for the presence of non-ischemic encephalopathy brain injuries and conditions, and sepsis at baseline incorporating adjustment of site as a random effect.

§ The primary outcome was favorable neurological outcome measured with the Extended Glasgow Outcome Scale (GOS-E) at 180 days post randomization. To enable alignment in effect direction between mortality and GOS-E, data are presented showing the proportion of patients with an unfavorable outcome rather than a favorable one. Primary outcome data were available for XX patients (XX.X%) in the conservative-oxygen group and XX patients (XX.X%) in the liberal-oxygen group.

|| Day 180 mortality data were available for XX patients (XX.X%) in the conservative-oxygen group and XX patients (XX.X%) in the liberal-oxygen group.

¶ Quality of life was assessed using the EQ-5D-5L; this scale evaluates mobility, self-care, usual activities, pain or discomfort, and anxiety and depression, with categorization of each of these dimensions into five levels that range from no problems to extreme problems. The EQ-5D-5L was converted to an EQ utility score, which ranges from -0.6 to 1.0, with 1.0 indicating the best health state. Patients who died were assigned a score of zero.

** MoCA-Blind data were available for XX patients (XX.X%) in the conservative-oxygen group and XX patients (XX.X%) in the liberal-oxygen group. The percentages include patients who died and were assigned a score of zero.

Abbreviations: Ci: confidence interval; EQ: EuroQol; GOS-E: Extended Glasgow Outcome Scale; ICU: intensive care unit; MoCA-Blind: Montreal Cognitive Assessment-Blind; IQR: interquartile range; SpO₂: arterial oxygen saturation as measured by pulse oximetry.

Table S9: Additional Analyses of Primary Outcome*				
	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)	Between-Group Difference†	Relative risk‡ (95% CI)
Primary outcome				
Unfavorable functional outcome at day 180§, n (%)				
Primary analysis	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis #1: adjustments for additional prespecified covariates				x.xx (x.xx to x.xx)
Sensitivity analysis #2: analysis as an ordinal outcome				x.xx (x.xx to x.xx)
Sensitivity analysis #3: complete case analysis	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis #4: eligible patients only	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Sensitivity analysis #5: eligible patients who received treatment	x (x.xx)	x (x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* The widths of the confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† The between-group difference in the primary outcome and the difference in percentage of patients discharged home was calculated using binomial regression with an identity link. Between group differences in duration of mechanical ventilation, and ICU and hospital lengths of stay were calculated as a ratio of geometric means.

‡ Relative risks were calculated using log-binomial models except for sensitivity analysis #2 which used ordinal regression.

§ The primary analysis incorporated adjustment for the presence of non-HIE brain injuries and conditions, and sepsis at baseline as well as for site as a random effect. Missing outcome data were imputed. Additional adjustments were incorporated for age, cardiac arrest location outside hospital, shockable first monitored rhythm, time to return of spontaneous circulation, whether there was a medical cause for arrest, and whether the patient had a STEMI in sensitivity analysis 2. Sensitivity analysis #3 replicated the primary analysis but was limited to patients where primary outcome data were available. Sensitivity analysis 4 excluded patients who were not eligible for the study who were inadvertently randomized. Sensitivity analysis #5 excluded ineligible patients and eligible patients who never received their randomized treatment.

Abbreviations: CI: confidence interval

Table S10: Cause-specific mortality at 180 days*

Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Neurological cause of death – n (%)		
Neurological death with or without brain death	xxx (xx.x)	xxx (xx.x)
Cardiovascular cause of death – n (%)		
Arrhythmia	xxx (xx.x)	xxx (xx.x)
Cardiovascular shock	xxx (xx.x)	xxx (xx.x)
Distributive (Septic) shock	xxx (xx.x)	xxx (xx.x)
Hypovolemic	xxx (xx.x)	xxx (xx.x)
Respiratory – n (%)		
Hypoxic respiratory failure	xxx (xx.x)	xxx (xx.x)
Metabolic – n (%)		
Metabolic	xxx (xx.x)	xxx (xx.x)
Other – n (%)		
Other	xxx (xx.x)	xxx (xx.x)

Table S11: Quality of life and cognitive function at 180 days*

Characteristic	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)
Mobility – n (%)		
No problems with walking around	xxx (xx.x)	xxx (xx.x)
Slight problems with walking around	xxx (xx.x)	xxx (xx.x)
Moderate problems with walking around	xxx (xx.x)	xxx (xx.x)
Severe problems with walking around	xxx (xx.x)	xxx (xx.x)
Unable to walk around	xxx (xx.x)	xxx (xx.x)
Self care – n (%)		
No problems with washing or dressing	xxx (xx.x)	xxx (xx.x)
Slight problems with washing or dressing	xxx (xx.x)	xxx (xx.x)
Moderate problems washing or dressing	xxx (xx.x)	xxx (xx.x)
Severe problems with washing or dressing	xxx (xx.x)	xxx (xx.x)
Unable to wash or dress	xxx (xx.x)	xxx (xx.x)
Usual activities (e.g. work, study, housework, family or leisure activities) – n (%)		
No problems with usual activities	xxx (xx.x)	xxx (xx.x)
Slight problems with usual activities	xxx (xx.x)	xxx (xx.x)
Moderate problems with usual activities	xxx (xx.x)	xxx (xx.x)
Severe problems with usual activities	xxx (xx.x)	xxx (xx.x)
Unable to do usual activities	xxx (xx.x)	xxx (xx.x)
Pain / discomfort – n (%)		
No pain / discomfort	xxx (xx.x)	xxx (xx.x)
Slight pain / discomfort	xxx (xx.x)	xxx (xx.x)
Moderate pain / discomfort	xxx (xx.x)	xxx (xx.x)
Severe pain / discomfort	xxx (xx.x)	xxx (xx.x)
Extreme pain / discomfort	xxx (xx.x)	xxx (xx.x)
Anxiety / depression – n (%)		
No anxiety / depression	xxx (xx.x)	xxx (xx.x)
Slight anxiety / depression	xxx (xx.x)	xxx (xx.x)
Moderate anxiety / depression	xxx (xx.x)	xxx (xx.x)
Severe anxiety / depression	xxx (xx.x)	xxx (xx.x)
Extreme anxiety / depression	xxx (xx.x)	xxx (xx.x)
MoCA-Blind, – mean ± SD		
	xx±xx	xx±xx
Died – no. (%)	xxx (xx.x)	xxx (xx.x)
Cognitively impaired– n (%)	xxx (xx.x)	xxx (xx.x)
Not cognitively impaired– n (%)	xxx (xx.x)	xxx (xx.x)

* Quality of life was assessed with the EQ-5D-5L, a generic preference-based health status instrument, which is comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression⁴. Cognition was assessed with the Montreal Cognitive Assessment-Blind (MoCA-Blind)⁵. The MoCA-Blind assesses cognition in domains of attention, memory, language, abstraction, and orientation. The maximum score is 22, with higher scores indicating better cognitive performance; a score of 18 or greater is typically considered normal. An extra point was added for patients who scored less than 22 and who had 12 years or less of formal education. There were XXX patients alive at day 180 (XXX in the conservative-oxygen group and XXX in the liberal-oxygen group). EQ-5D-5L data were available for XXX of these patients (XXX in the conservative-oxygen group and XXX in the liberal group) and MoCA-blind data were available for XXX of these patients (XXX in the conservative-oxygen group and XXX in the liberal group).

Abbreviations: EQ5D5L: EQ5D 5 levels; MoCA-Blind: Montreal Cognitive Assessment-Blind; SD: standard deviation.

Table S12: Additional Analyses Secondary Outcomes*			
Outcome	Conservative oxygen (n=XXX)	Liberal oxygen (n=XXX)	Effect estimate (95% CI)†
Geometric mean duration of mechanical ventilation, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Geometric mean duration of mechanical ventilation for survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean duration of mechanical ventilation, for non-survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean ICU length of stay, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Geometric mean ICU length of stay for survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean ICU length of stay for non-survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean hospital length of stay, days (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Geometric mean hospital length of stay for survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Geometric mean hospital length of stay, for non-survivors, hours (95% CI)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Median quality of life EQ utility score¶ (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median patient / proxy reported health state scale** (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median MoCA-Blind†† (IQR)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* The widths of the confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† Effect estimates were calculated as the ratio of geometric means for patients allocated to conservative vs. liberal oxygen for the duration outcomes; survivor average causal effects are presented for EQ utility score, EQ visual analogue scale, and MOCA-Blind.

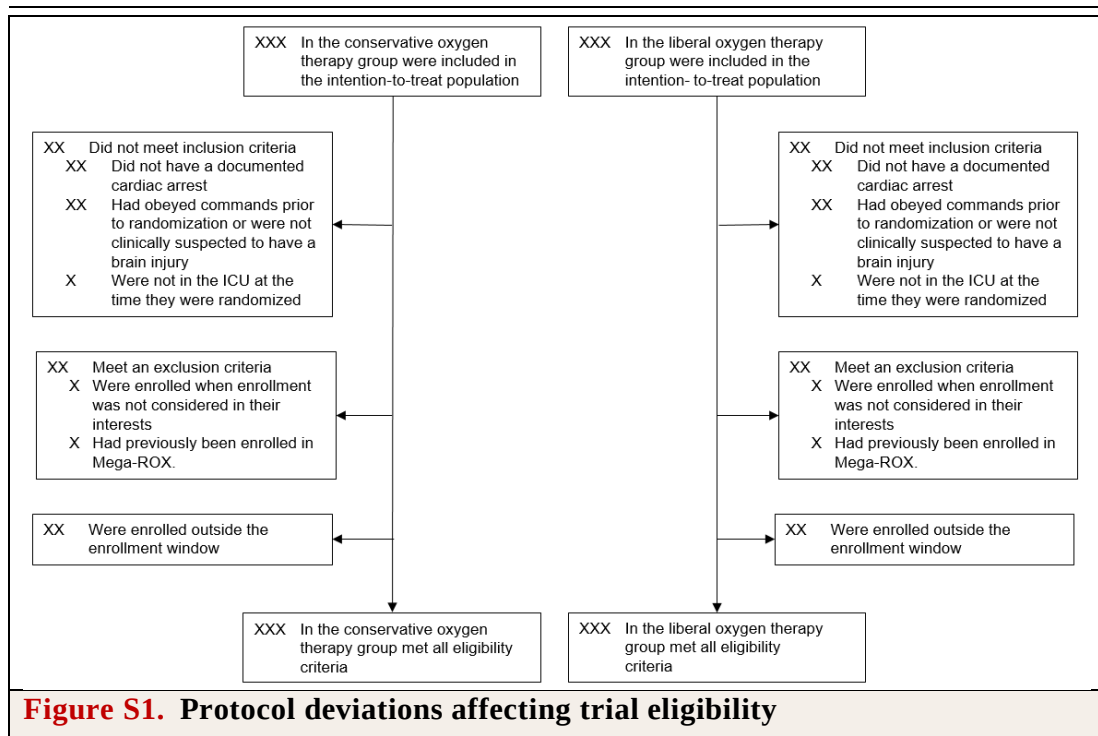
¶ Quality of life was assessed using the EQ-5D-5L; this scale evaluates mobility, self-care, usual activities, pain or discomfort, and anxiety and depression, with categorization of each of these dimensions into five levels that range from no problems to extreme problems. The EQ-5D-5L was converted to an EQ utility score, which ranges from -0.6 to 1.0, with 1.0 indicating the best health state.

** The patient's health state was rated using the EQ visual analogue scale which ranges from 0 to 100 where 0 is described as "the worst health state you can imagine" and 100 described as "the best health state you can imagine."

†† The MoCA-Blind assesses cognition in domains of attention, memory, language, abstraction, and orientation. The maximum score is 22, with higher scores indicating better cognitive performance; a score of 18 or greater is typically considered normal. An extra point was added for patients who scored less than 22 and who had 12 years or less of formal education.

Abbreviations: CI: confidence interval; EQ: EuroQol; IQR: interquartile range; MoCA-Blind: Montreal Cognitive Assessment-Blind.

38. Supplementary figures



Abbreviations: LOGICAL: Low Oxygenation Goals in Cardiac Arrest injury Limitation; ICU: Intensive Care Unit; Mega-ROX: Mega Randomized Registry Trial Research Program.

