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Original Article

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)

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ABSTRACT

Background: The effect of conservative vs. liberal oxygen therapy on 90-day in-hospital mortality in adults with hypoxic ischaemic encephalopathy (HIE) following a cardiac arrest who are receiving invasive mechanical ventilation in the intensive care unit (ICU) is uncertain.
Objective: To summarise the protocol and statistical analysis plan for the Mega-ROX HIE trial.
Design, setting and participants: Mega-ROX HIE is an international randomised clinical trial that will be conducted within an overarching 40,000-participant registry-embedded clinical trial comparing

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Protocol

conservative and liberal ICU oxygen therapy regimens. We expect to enrol approximately 4000 participants with suspected HIE following a cardiac arrest who are receiving invasive mechanical ventilation in the ICU.

Main outcome measures: The primary outcome is in-hospital all-cause mortality up to 90 days from the date of randomisation. Secondary outcomes include duration of survival, duration of mechanical ventilation, ICU length of stay, hospital length of stay, and the proportion of participants discharged home.

Results and conclusions: Mega-ROX HIE will compare the effect of conservative vs. liberal oxygen therapy regimens on day-90 in-hospital mortality in adults in the ICU with suspected HIE following a cardiac arrest. The protocol and planned analyses are reported here to mitigate analysis bias.

Trial registration: Australian and New Zealand Clinical Trials Registry (ACTRN 12620000391976).

Patients who are unconscious after resuscitation from cardiac arrest are at risk of hypoxic ischaemic encephalopathy. The pathophysiological basis of this condition is whole-brain ischaemia followed by a reperfusion injury.[1] The reperfusion injury occurs because of an imbalance between oxygen-free radicals and endogenous antioxidants called oxidative stress.[1] Because people who are unconscious after resuscitation from a cardiac arrest usually require a period of invasive mechanical ventilation in the intensive care unit (ICU) during which supplemental oxygen is administered, the potential for conservative use of oxygen in the ICU to reduce oxidative stress in the brain and mitigate secondary brain damage is of interest.[2]

The potential beneficial effects of conservative ICU oxygen therapy were highlighted in a subgroup analysis[3] of post-cardiac arrest patients who were enrolled in the *Intensive Care Unit Randomised Oxygen* (ICU-ROX) trial.[4] In particular, in 166 ICU-ROX participants with suspected hypoxic ischaemic encephalopathy following cardiac arrest, day 180 mortality was significantly lower among those assigned to conservative oxygen therapy than it was among those assigned to liberal oxygen therapy. In contrast, in the *Blood Pressure and Oxygenation Targets in Postresuscitation Care* (BOX) trial,[5] conservative oxygen therapy did not significantly reduce the proportion of patients who died in hospital or were discharged from hospital with severe disability or coma compared to liberal oxygen therapy. The conservative oxygen therapy regimen evaluated in the BOX trial[5] was more liberal than was used in the ICU-ROX trial,[4] and many patients allocated to conservative oxygen therapy were exposed to an arterial oxygen tension (PaO_2) of greater than 100 mmHg in the first 6 h after randomisation.[5] This exposure to hyperoxaemia in patients allocated conservative oxygen therapy may have been sufficient to cause harm and might, therefore, have limited potential benefits of this treatment regimen.

To address the uncertainty about the effect of conservative oxygen therapy on survival in patients at risk of hypoxic ischaemic encephalopathy after resuscitation from cardiac arrest, we are conducting the Mega-ROX hypoxic ischaemic encephalopathy (HIE) (Mega-ROX HIE) trial. This trial will test the hypothesis that conservative oxygen therapy compared with liberal oxygen therapy decreases in-hospital all-cause mortality up to 90 days after randomisation. Here we present the protocol and statistical analysis plan for Mega-ROX HIE.

1. Methods

1.1. Trial design

Mega-ROX HIE is a phase three international, multicentre, randomised, two-sided superiority trial designed to test the hypothesis that among adult ICU patients with suspected HIE receiving invasive ventilation, conservative oxygen therapy compared to liberal oxygen therapy reduces in-hospital all-cause mortality up to 90 days from the date of randomisation. It has been designed with reference to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.[6] Mega-ROX HIE is one of three nested trials being conducted within an overall 40,000 participant sample size envelope as part of the Mega-ROX trial research program. The protocol and statistical analysis plan for the overarching Mega-ROX trial and for the nested Mega-ROX Sepsis and Mega-ROX Brains trials have been reported previously.[7–9]

We plan to present data from the Mega-ROX HIE trial in a stand-alone manuscript because this nested study has sufficient size to detect a plausible treatment effect of conservative oxygen therapy on in-hospital mortality in this subgroup of patients.[2] Nested within the Mega-ROX HIE trial, in a subset of >40 Mega-ROX ICUs in Australia, New Zealand, and Ireland, we are conducting the Low OxyGen Intervention for Cardiac Arrest injury Limitation trial (LOGICAL).[10] The protocol and statistical analysis plan for the LOGICAL trial, which will test the hypothesis that conservative oxygen therapy compared with liberal oxygen therapy increases survival with a favourable neurological outcome at day 180, have been published previously.[10] The in-hospital mortality data from the Mega-ROX HIE cohort should complement the longer-term survival and functional outcome data from the LOGICAL trial data.

1.2. Setting and population

Mega-ROX HIE will be conducted in approximately 100 ICUs worldwide and is expected to include patients from a range of low, middle, and high-income countries. Patients ≥18 years who are receiving invasive mechanical ventilation in the ICU following a cardiac arrest and are suspected of having HIE (i.e. have not obeyed commands following the return of spontaneous circulation where there is clinical concern about possible brain damage) will be eligible for inclusion. Where enrolment is not considered to be in a patient's best interests by the treating clinician, they will be excluded. Operationally, this criterion will exclude all patients where either of the oxygen regimens being tested is considered clinically indicated or contraindicated, and situations where death is deemed imminent and inevitable. Patients who have previously been enrolled in the study will also be excluded. Patients must be enrolled within 12 h of fulfilling the eligibility criteria. When a patient is not enrolled within this timeframe, they will be counted as “missed” rather than “excluded” for the purposes of describing participant flow.

Our pragmatic eligibility criteria are designed to ensure that the trial population includes all patients with suspected HIE following a cardiac arrest where therapeutic decisions about oxygen therapy are made in clinical practice, irrespective of the specific cause of the arrest.

1.3. Randomisation and blinding

Treatment assignment will be performed using a secure, centralised, web-based randomisation interface. Participants will be enrolled in the study by ICU doctors, nurses, and research staff. The assigned intervention will be communicated to the bedside nurse and/or respiratory therapist, who will implement the study intervention. One novel feature of this trial is that it will use adaptive randomisation to subtly increase the probability that trial participants are allocated to the oxygen regimen that appears to be associated with the lowest mortality risk based on available data at interim analyses. Randomisation ratios of 1.05:1 in favour of liberal oxygen therapy, 1:1.05 in favour of conservative oxygen therapy, and 1:1 may all be used at different times of the Mega-ROX HIE trial. Other randomisation ratios will not be used. The method by which the randomisation ratio that applies to individual participants is determined is outlined in the protocol manuscript for the overarching Mega-ROX trial program.[7]

1.4. Study treatments

The Mega-ROX trial program is designed to compare two approaches to oxygen therapy that are within the spectrum of current usual practice. For Mega-ROX HIE, conservative oxygen therapy is defined as the *intervention* and will be compared with a *control arm* of liberal oxygen therapy. The details of these approaches have been outlined in the protocol manuscript for the overarching Mega-ROX trial program.[7] In brief, in participants allocated to conservative oxygen therapy, the lowest possible FIO_2 to achieve an SpO_2 of $\geq$91% will be used. In this group, SpO_2 levels greater than 94% will be strictly avoided, and an upper SpO_2 alarm limit of 95% will apply whenever supplemental oxygen is being administered in the ICU to minimise the risk of hyperoxaemia. For participants allocated to liberal oxygen therapy, oxygen will be delivered as directed by the treating clinician, with the caveat that the minimum FIO_2 allowed while the participant is invasively mechanically ventilated will be 0.30.

The duration of study therapy will be until ICU discharge or 90 days, whichever is sooner. The study intervention will be applied in the ICU only. If, during the course of their ICU admission, participants are transported outside of the ICU for radiological or other investigations or for procedures or operations, they may receive standard (non-study) treatment. Similarly, if an increase in FIO_2 is required for procedures performed in the ICU, including (but not limited to) bronchoscopy, suctioning, tracheostomy, or preparation for extubation, this is permitted in both groups. There are no restrictions on concomitant treatments provided to participants, such as the amount of positive end expiratory pressure (PEEP) used.

1.5. Outcomes

The primary outcome is in-hospital all-cause mortality up to 90 days from the date of randomisation. All participants who survive the index hospital admission and are discharged from that hospital within 90 days of randomisation will be defined as alive.

Secondary outcomes are duration of survival time up until the last follow-up, ICU length of stay, hospital length of stay, duration of invasive mechanical ventilation, the proportion of participants discharged home, and day-90 all-cause mortality, which will be reported for participants where vital status after hospital discharge can be obtained from registry data sources (for example, a national death registry).

1.6. Data collection and management

Mega-ROX HIE will use a combination of trial-specific data and existing registry data sources. Specific details of the data sources that will be used and the data management process are reported in the protocol manuscript for the overarching Mega-ROX trial program.[7] Notably, important baseline predictors of outcome in cardiac arrest patients, including time to return spontaneous circulation and initial rhythm, were not collected in the Mega-ROX trial;[7] however, these variables will be available for the subset of 1400 patients included in the LOGICAL trial.[10]

1.7. Ethics approval

Research ethics approval will be obtained prior to the start of the study at each institution from the responsible local and/or national human research ethics committee. Specific consent processes that will be used are described in the protocol manuscript for the overarching Mega-ROX trial program.[7]

1.8. Data monitoring committee

An independent data monitoring committee (DMC) consisting of experts in intensive care medicine, clinical research, and biostatistics was established before the first trial participant was enrolled. The DMC members are Prof Anders Perner (Chair), Prof. Manu Shankar-Hari, and Prof. Laurent Billot (DMC statistician). The specific responsibilities of the DMC are outlined in a set of DMC guidelines and a DMC charter, which was prepared by the study management committee and signed by the members of the DMC before the trial commenced.

The timing of interim analyses for Mega-ROX HIE will be determined by the overall recruitment rate in the overarching trial program. In particular, interim analyses for efficacy will occur after every 8000 trial participants are enrolled in the overarching trial. These interim analyses will require the DMC to provide advice to the management committee about both the overarching Mega-ROX trial and about nested studies, including Mega-ROX HIE. However, as shown in Fig. 1, an interim analysis for Mega-ROX HIE participants specifically will only occur where there is evidence of heterogeneity of treatment response for participants with versus without HIE ($P < 0.05$). If such an analysis is undertaken, stopping rules will be determined by a Haybittle-Peto boundary of $p < 0.001$.

1.9. Sample size and power

The specific sample size of Mega-ROX HIE will be determined by the proportion of participants in the overarching Mega-ROX trial who are identified as having suspected HIE at baseline. Based on the proportion of participants with these conditions included in the ICU-ROX trial (17.2%),[4] Mega-ROX HIE was originally expected to recruit $\approx$6880 participants. Assuming a baseline in-hospital mortality rate of 54.4% in patients with HIE, this sample size would provide >90% power to detect an absolute mortality difference of 4 percentage points (i.e. a reduction to 50.4%) using a two-tailed significance level of 0.05. This effect size is smaller than the treatment effect suggested by observed point estimates in the ICU-ROX trial[3] and is, thus, appropriately conservative. A total of 1261 of the first 12529 participants in the Mega-ROX trial (10.1%) fulfilled eligibility criteria for the Mega-ROX HIE trial, a rate that, if sustained for the rest of the trial, would translate to a Mega-ROX HIE

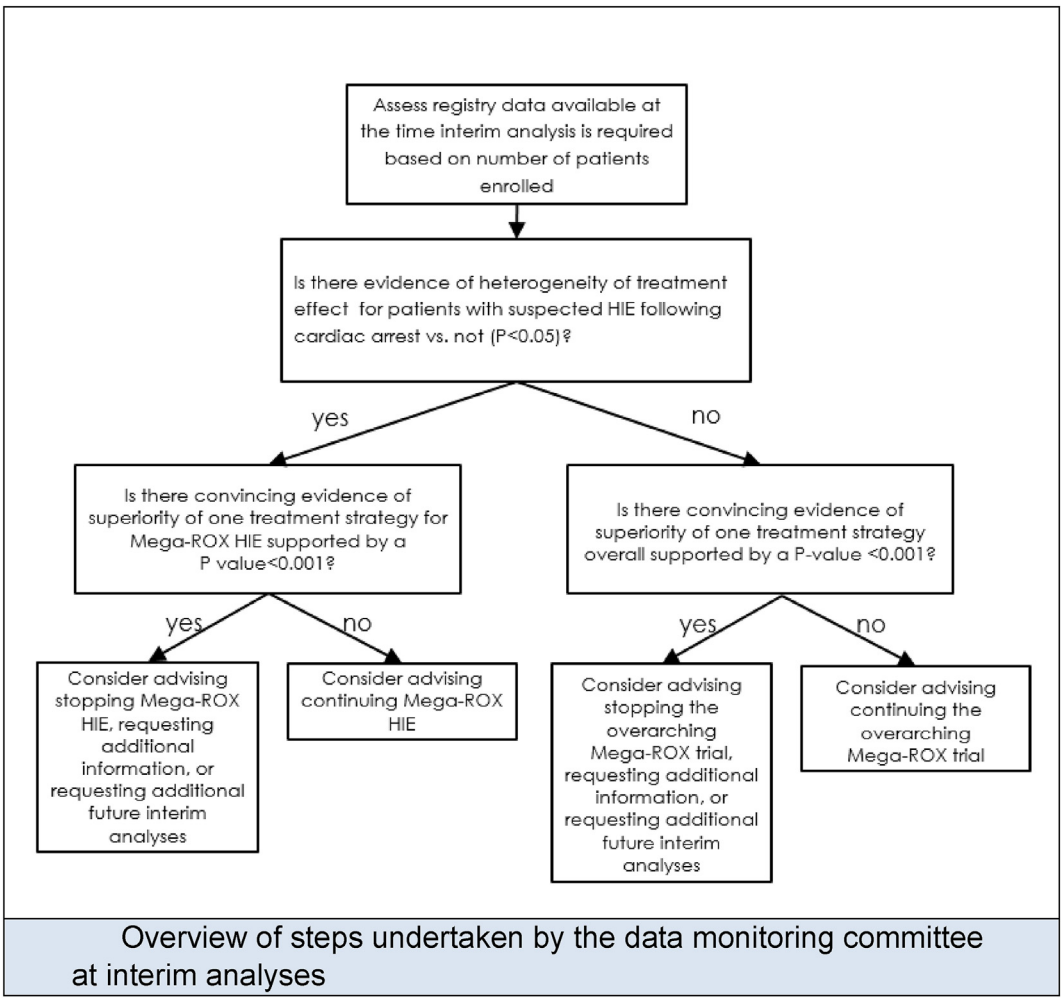

Fig. 1. Overview of steps undertaken by the data monitoring committee at interim analyses. Abbreviations: HIE: hypoxic ischaemic encephalopathy; Mega-ROX: Mega randomised registry trial comparing two approaches to oxygen therapy in the intensive care unit.

sample of ≈4000 participants. Table 1 summarises a range of potential scenarios for sample size and power for Mega-ROX HIE. We will update the Australian and New Zealand Clinical Trials Registry with the anticipated final sample size for Mega-ROX HIE, based on the proportion of participants with HIE recruited at the time of the 4th interim analysis.

1.10. Overview of planned statistical analyses

We will analyse data on an intention-to-treat basis, whereby all participants assigned to a treatment group will be analysed according to the group to which they were assigned, without imputation of missing data except where prespecified. The intention to treat population will be defined as all participants enrolled in the trial except for those whose consent for the use of study data is either not provided or withdrawn. A P-value less than 0.05 (two-tailed) will be used to indicate statistical significance for the primary outcome variable. For the six secondary clinical outcomes, we will control the family-wise error rate at 5% by applying a Holm-Bonferroni correction. All analyses will be performed using Stata v17.0 or later (Stata Statistical Software, College Station, TX, USA). The reporting of the study will align with the CONSORT statement.[11]

The study team includes a blinded statistician who is a member of the study management committee and an unblinded statistician who is independent of the study management committee. The unblinded statistician will conduct interim analyses and provide these to the DMC. Once study data are available for the entire study population, the unblinded study statistician will assign mock treatment codes to study participants. Analyses using actual study data but with mock treatment codes will be run by the blinded statistician using the general approach outlined in this document. Any data queries that arise from these initial analyses will be addressed. Any changes that are needed to the approach outlined here will be specified in the formal stand-alone statistical analysis plan, which will be publicly available prior to the final study database lock or the unmasking of actual study treatment assignments. Analyses of the final study dataset will be undertaken by two study statisticians independently, with any discrepancies between findings resolved through consensus and discussion with the management committee when required.

1.10.1. Analyses of the primary outcome

Analysis of the primary outcome (in-hospital mortality by day 90) and other binary outcomes will be via log-binomial models, adjusting for non-HIE brain injuries/conditions and sepsis. These characteristics will be included in the model because participants with these diagnoses will also be included in the Mega-ROX Brains and Mega-ROX Sepsis studies, so there is potential for imbalance in

Table 1
Potential scenarios for sample size and power for Mega-ROX HIE.

Control event rate[a]	Sample size	Absolute mortality effect (i.e. percentage reduction) detectable with 90% power and 2-sided significance level of 0.05
40%	4000	4.96
40%	4500	4.68
40%	5000	4.44
40%	5500	4.24
40%	6000	4.06
40%	6500	3.90
40%	7000	3.76
45%	4000	5.06
45%	4500	4.78
45%	5000	4.53
45%	5500	4.32
45%	6000	4.14
45%	6500	3.98
45%	7000	3.84
50%	4000	5.12
50%	4500	4.82
50%	5000	4.58
50%	5500	4.37
50%	6000	4.18
50%	6500	4.02
50%	7000	3.87
55%	4000	5.12
55%	4500	4.82
55%	5000	4.58
55%	5500	4.36
55%	6000	4.18
55%	6500	4.01
55%	7000	3.87
60%	4000	5.07
60%	4500	4.77
60%	5000	4.53
60%	5500	4.32
60%	6000	4.13
60%	6500	3.97
60%	7000	3.82

[a] The control event rate is assumed in-hospital all-cause mortality up to 90 days from the date of randomisation in participants allocated to liberal oxygen therapy (the comparator arm). No loss to follow up is assumed.

these characteristics across arms of Mega-ROX HIE. The numbers at risk in each group and the number and proportion of events observed will be reported, as well as the equivalent absolute risk difference, relative risk ratio, and corresponding 95% CI. Sensitivity analyses accounting for differences across sites and any clinically meaningful baseline imbalances will be performed using log-binomial regression. In addition, we will incorporate adjustments for the independent covariates of age, sex, and illness severity. The main sensitivity analyses for the impact of missing primary outcomes will involve imputing outcomes under "worst-best" and "best-worst" case scenarios. In the "worst-best" scenario, a "worst" outcome event (i.e. in-hospital death within 90 days) is assigned to all participants missing the outcome in one treatment group, and a "best" outcome event (i.e. survival to hospital discharge within 90 days) is assigned to all participants missing the outcome in the other treatment group. The "best-worst" scenario is the exact opposite assignment of outcomes. If substantively different conclusions do not arise from these two analyses, then no further missing data assessments will be performed for that outcome. If a substantively different conclusion does arise, then multiple imputation will be undertaken. Missing outcomes will be imputed separately by randomised group, using chained equations and predictive mean matching, using the five nearest neighbours.

In some low- and middle-income countries participating in this study, participants are sometimes discharged from the ICU (to home) when discharge is not considered medically indicated (e.g. where a decision is taken by the family or the patient to leave the hospital against medical advice, for example, because of the high cost of care and/or because death is anticipated). We will undertake two sensitivity analyses to account for participants categorised as discharged from the ICU when discharge was not considered medically indicated. In the first analysis, these participants, when assigned to conservative oxygen, will be defined as dead and, when assigned to liberal oxygen, will be defined as alive. In the second analysis, these participants, when assigned to conservative oxygen, will be defined as alive and, when assigned to liberal oxygen, will be defined as dead.

1.10.2. Analyses of secondary outcomes

The effect of treatment allocation on the proportion of participants discharged home and the proportion of participants dying by day 90 will be assessed in the same way as the primary outcome. To account for the competing risk of death, ICU and hospital lengths of stay and hours until removed from invasive mechanical ventilation will be analysed using sub-distribution hazard regression models and presented using cumulative incidence functions. As lengths of stay are typically well approximated by log-normal distributions, for increased transparency, they will also be reported as geometric means (95% CI), with additional stratification for survival and differences between groups reported as a ratio (95% CI). Survival time according to treatment group will be displayed as Kaplan–Meier curves and analysed using a log-rank test. Estimates of hazard ratios for survival, with corresponding 95% CI and P values, will be obtained from the Cox proportional hazards models incorporating treatment group and non-HIE brain injuries/conditions and sepsis, and additionally using independent covariates used in the multivariable logistic models described in relation to the primary outcome. The assumption of proportional hazards will be assessed, and if violated, the log-rank test will be used to compare survival times between treatment groups.

1.10.3. Analyses of oxygen exposure metrics

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 PaO_2 thresholds, 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, medians, and 95% CIs using quantile regression.

Analyses that compare the proportion of participants 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. 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% confidence intervals.

1.11. Presentation of outcome data

The planned presentation of baseline data is shown in Table 2. Exposure to oxygen by treatment group will be described as shown in Table 3. Primary and secondary outcome data will be presented as shown in Table 4.

The proposed list of main manuscript figures is as follows:

1. Fig. 1: Participant flow diagram. Description: Participant flow diagram.
2. Figure 2: Kaplan–Meier survival estimates of the probability of survival to day 90. Description: A line graph with days 0–90 on the horizontal axis and the probability of survival on the vertical axis.

Table 2
Proposed presentation of baseline characteristics table.

Characteristic	Conservative oxygen therapy (n = xxx)	Liberal oxygen therapy (n = xxx)
Age – yr	xx ± xx.x	xx ± xx.x
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Body mass index	xx.x ± xx	xx.x ± xx
Clinical frailty score	xxx (xx.x)	xxx (xx.x)
Source of admission to ICU – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)
Hours from hospital admission to randomisation	xx.x ± xx	xx.x ± xx
Hours from ICU admission to randomisation	xx.x ± xx	xx.x ± xx
APACHE-II score[a]	xx.x ± xx	xx.x ± xx
SAPS-III score[b]	xx.x ± xx	xx.x ± xx
Diagnosis – no. (%)[c]		
Diagnosis #1	xxx (xx.x)	xxx (xx.x)
Diagnosis #2	xxx (xx.x)	xxx (xx.x)
Diagnosis #3	xxx (xx.x)	xxx (xx.x)
Diagnosis #4	xxx (xx.x)	xxx (xx.x)
Diagnosis #5	xxx (xx.x)	xxx (xx.x)
Baseline oxygen data		
FiO_2	xx.x ± xx	xx.x ± xx
PaO_2 – mmHg	xx.x ± xx	xx.x ± xx
PaO_2/FiO_2 ratio – mmHg	xx.x ± xx	xx.x ± xx

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not approximately symmetric, the median [IQR] will be reported instead of mean ± SD). To facilitate meaningful interpretation of categorical variables, categories with small numbers (<10) will be collapsed for analysis.
Abbreviations: APACHE: Acute Physiology And Chronic Health Evaluation; CNS: Central Nervous System; ICU: Intensive Care Unit; OT: operating theatre; SpO_2: arterial oxygen saturation on pulse oximetry; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; PEEP: positive end expiratory pressure.
[a] Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
[b] Scores on the SAPS-III range from 0 to 217, with higher scores indicating more severe disease. The SAPS-III score was collected from trial participants from Brazil.
[c] Common diagnostic categories based on the ICU admission diagnosis that will be presented will be prespecified based on a review of pooled data prior to the unblinding of treatment allocation. While some patients may be identified as having an ICU admission diagnosis of hypoxic brain damage, many other diagnoses, including acute myocardial infarction and ventricular fibrillation, might also be specified.

The proposed list of main manuscript supplemental figures is as follows:

1. Figure S1A: Mean FiO_2 by treatment group. Description: Line graph with days 0–7 on the horizontal axis and FiO_2 on the vertical axis, with mean daily FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily FiO_2 will be calculated from recordings of FiO_2 taken six hourly while the participant is invasively ventilated in the ICU up until day 7. Data points will be reported with corresponding standard error bars.
2. Figure S1B: Highest FiO_2 by treatment group. Description: Line graph with days 0–7 on the horizontal axis, and FiO_2 on the vertical axis with the highest daily FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The highest FiO_2 will be recorded daily while the participant is invasively ventilated in the ICU up until day 7. Data points will be reported with corresponding standard error bars.
3. Figure S1C: Lowest FiO_2 by treatment group. Description: Line graph with days 0–7 on the horizontal axis and FiO_2 on the vertical axis, with the lowest daily FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The lowest FiO_2 will be recorded daily while the participant is invasively ventilated in the ICU up until day 7. Data points will be reported with corresponding standard error bars.
4. Figure S2A: Mean daily PaO_2 by treatment group. Description: Line graph with days 0–7 on the horizontal axis and PaO_2 on the vertical axis, with mean daily PaO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily PaO_2 will be calculated from recordings of PaO_2 taken six hourly while the participant is in the ICU up until day 7. Data points will be reported with corresponding standard error bars.
5. Figure S2B: Highest daily PaO_2 by treatment group. Description: Line graph with days 0–7 on the horizontal axis and PaO_2 on the vertical axis, with the highest daily PaO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The highest PaO_2 will be recorded daily while the participant is in the ICU up until day 7. Data points will be reported with corresponding standard error bars.
6. Figure S2C: Lowest PaO_2 by treatment group. Description: Line graph with days 0–7 on the horizontal axis and PaO_2 on the vertical axis, with the lowest daily PaO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The lowest PaO_2 will be recorded daily while the participant is in the ICU up until day 7. Data points will be reported with corresponding standard error bars.

1.12. Subgroup analyses

We will evaluate for heterogeneity of treatment effect for patients admitted to the ICU from the emergency department vs. admitted to the ICU from elsewhere by fitting an interaction

Table 3
Proposed presentation of oxygen exposure by treatment group.

Oxygen exposure metric – n (%)	Conservative oxygen therapy (n = xxx)	Liberal oxygen therapy (n = xxx)	Between-Group difference (95% CI)
Median [IQR] percentage of hours per participant SpO_2 ≥97%	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Median [IQR] number of hours per participant SpO_2 ≥97%	xx (xx.x)	xx (xx.x)	xx (xx to xx)
Median [IQR] percentage of hours per participant SpO_2 <88%	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Median [IQR] number of hours per participant SpO_2 <88%	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Proportion of participants with at least one PaO_2 recording <60 mmHg	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Proportion of participants with at least one PaO_2 recording >100 mmHg	xx (xx.x)	xx (xx.x)	xx (xx to xx)
Median [IQR] percentage of hours per participant FIO_2 0.21	xx (xx.x)	xx (xx.x)	xx (xx to xx)
Median [IQR] number of hours per participant FIO_2 0.21	xx (xx.x)	xx (xx.x)	xx (xx to xx)

Abbreviations: IQR: Interquartile range; CI: Confidence Interval.

Table 4
Proposed presentation of outcomes.

	Conservative oxygen therapy (n = xxx)	Liberal oxygen therapy (n = xxx)	Estimate (95% CI)
Primary outcome[a]			
Died at the hospital by day 90- no. (%)	xxx (xx.x)	xxx (xx.x)	**Relative risk** xx (xx to xx) **Risk difference** xx (xx to xx)
Secondary outcomes			
Hours until removed alive from invasive mechanical ventilation			**Subhazard ratio of time to extubation**[c]
Number of patients	xxx	xxx	
Median (IQR)[b]	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Days until discharged alive from ICU			**Subhazard ratio of time to ICU discharge**[c]
Number of participants	xxx	xxx	
Median (IQR)[b]	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Days until discharged alive from hospital			**Subhazard ratio of time to hospital discharge**[c]
Number of participants	xxx	xxx	
Median (IQR)[b]	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Discharged home- no. (%)	xxx (xx.x)	xxx (xx.x)	**Relative risk** xx (xx to xx) **Risk difference** xx (xx to xx)
Day-90 mortality- no. (%)	xxx (xx.x)	xxx (xx.x)	**Relative risk** xx (xx to xx) **Risk difference** xx (xx to xx)

Abbreviations: IQR: Interquartile range; CI: Confidence Interval.
[a] A P-value for the primary outcome comparison will be shown in a footnote. The absolute difference in 90-day mortality and corresponding relative risk will be adjusted for site and for the presence or absence of each of the following at randomisation: suspected hypoxic ischaemic encephalopathy following resuscitation from a cardiac arrest, and sepsis.
[b] Duration of invasive mechanical ventilation, ICU, and hospital length of stay will be calculated from cumulative incidence functions, with mortality regarded as a competing risk.
[c] Ratios of median time to discharge (or extubation) will be estimated using censored linear regression with the logarithm of time to discharge (or extubation) as the dependent variable. Adjustments will be made for the same variables as for the primary outcome.

between treatment and subgroup for the primary outcome (day 90 in-hospital mortality).

2. Summary

Mega-ROX HIE is a phase three international, multicentre, randomised, two-sided superiority trial designed to test the hypothesis that among invasively ventilated adult ICU patients with suspected HIE following cardiac arrest, conservative oxygen therapy compared to liberal oxygen therapy reduces in-hospital all-cause mortality up to 90 days from the date of randomisation. This protocol and statistical analysis plan article was submitted for publication before recruitment was completed.

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Mega-ROX HIE is funded by grants from the Health Research Council of New Zealand and by an unrestricted donation from the Alpha Charitable Trust. In Canada, Mega-ROX has received funding from the Pragmatic Trials Platform—Alberta Strategy for Patient-Oriented Research (SPOR) Support Unit. The funding bodies have had no input into the design or conduct of the trial or into the statistical analysis plan and will have no input into the analysis or reporting of the results. The study is coordinated in New Zealand by the Medical Research Institute of New Zealand and in Australia by the Australian and New Zealand Intensive Care Research Centre. The study is coordinated in Brazil by the HCor Research Institute. The study is coordinated in Ireland by the Irish Critical Care Clinical Trials Network, which is supported by the Health Research Board. The study is coordinated in Canada by the University of Alberta. The study is coordinated in Japan by Jikei University. The study is coordinated in Asia by the Critical Care Asia Network and in Africa by the Critical Care Africa Network (part of the National Intensive Care Surveillance, Mahidol—Oxford Tropical Medicine Research Unit [NICS-MORU] collaboration), which is supported by a Wellcome Innovations grant (215522). This study is endorsed by the Australia and New Zealand Intensive Care Society Clinical Trials Group, the Irish Critical Care Clinical Trials Group, and the Alberta Health Services Critical Care Strategic Clinical Network. This study has been approved by the Japanese Intensive Care Research Group.

Conflict of interest

Rinaldo Bellomo, Paul Young, and Carol Hodgson, declare a conflict of interest as Editors or Editorial Committee members of this journal.

CRediT authorship contribution statement

Young: Conceptualisation, Methodology, Writing - original draft, Funding acquisition. **Al-Fares, Aryal, Arabi, Ashraf, de Oliveira Manoelo, Fujii, Hodgson, Landoni, Maia, Mangal, Mazlan, Nichol, Tirupakuzhi Vijayaraghavan:** Writing - review and editing. **Beane, Dullawe, Fazla, Haniffa, Hunt, Lawrence, Mackle, Olatunji, A Rashan, S Rashan:** Writing - review and editing, Project administration. **Bagshaw:** Funding acquisition, Writing - review and editing. **Kasza:** Methodology, Writing - review and editing.

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