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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 with nonhypoxic ischaemic acute brain injuries and conditions in the intensive care unit (Mega-ROX Brains)

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A B S T R A C T

Background: The effect of conservative vs. liberal oxygen therapy on 90-day in-hospital mortality in adults who have nonhypoxic ischaemic encephalopathy acute brain injuries and conditions and are receiving invasive mechanical ventilation in the intensive care unit (ICU) is uncertain.

Objective: The objective of this study was to summarise the protocol and statistical analysis plan for the Mega-ROX Brains trial.

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Stroke
Traumatic brain injury
Subarachnoid haemorrhage

Design, setting, and participants: Mega-ROX Brains is an international randomised clinical trial, which will be conducted within an overarching 40,000-participant, registry-embedded clinical trial comparing conservative and liberal ICU oxygen therapy regimens. We expect to enrol between 7500 and 9500 participants with nonhypoxic ischaemic encephalopathy acute brain injuries and conditions who are receiving unplanned invasive mechanical ventilation in the ICU.
Main outcome measures: The primary outcome is in-hospital all-cause mortality up to 90 d 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 Brains will compare the effect of conservative vs. liberal oxygen therapy regimens on 90-day in-hospital mortality in adults in the ICU with acute brain injuries and conditions. The protocol and planned analyses are reported here to mitigate analysis bias.
Trial Registration: Australian and New Zealand Clinical Trials Registry (ACTRN 12620000391976).

1. Introduction

Patients with acute brain injuries and conditions often receive invasive mechanical ventilation in the intensive care unit (ICU). In such patients, a liberal approach to oxygenation may be preferred because the brain is exquisitely sensitive to oxygen deprivation,[1] and liberal oxygen use provides a greater margin of safety against inadvertent hypoxaemia than that in more restrictive use. Even in the absence of hypoxaemia, brain oxygen tissue oxygenation may be reduced in brain-injured patients due to impaired cerebral autoregulation, raised intracranial pressure, and impaired microvascular function.[2] Low brain oxygen tissue oxygenation levels are associated with adverse outcomes in this setting and may be normalised by liberal administration of oxygen.[3] Liberal use of oxygen in brain-injured patients has potential risks as well as potential benefits. Use of a high fraction of inspired oxygen (FIO_2) is associated with cerebral oxidative stress in patients with traumatic brain injury (TBI)[4] and with vasospasm in patients with subarachnoid haemorrhage (SAH).[5] Patients with acute brain injuries and conditions often do not require supplemental oxygen to prevent hypoxaemia;[6] they are typically intubated to provide airway protection, rather than to treat respiratory failure. As these patients often have normal pulmonary gas exchange, they may be prone particularly to developing hyperoxaemia when oxygen is used liberally.

Further complexity is added because the optimal oxygen regimen may depend on the nature of the patient's brain injury. In a post hoc analysis of patients with acute brain pathologies enrolled in the *ICU Randomised Trial Comparing Two Approaches to Oxygen Therapy* (ICU-ROX),[7] we observed statistically significant heterogeneity in the effect of conservative vs. usual oxygen therapy on 180-day mortality in patients with hypoxic ischaemic encephalopathy (HIE) vs. patients with other acute brain injuries ($P = 0.02$).[6] This group of "other acute brain injuries" included patients with conditions including TBI, SAH, central nervous system infection, and stroke. Liberal oxygen appeared to harm patients with HIE and benefit patients with the other conditions mentioned. Such heterogeneity may reflect the fact that the pathophysiology of the former condition is characterised by global ischaemia and reperfusion.[8] Other than in patients with HIE,[9] the evidence base from clinical trials comparing liberal and conservative oxygen regimens in ICU patients with acute brain injuries and conditions is extremely limited.[6] In patients in the ICU-ROX trial with non-HIE acute brain injuries and conditions, the point estimate for the treatment effect on 180-day mortality favoured liberal oxygen therapy by 7.6 percentage points (95% confidence interval [CI], −4.6 to 19.9 percentage points).[6] An insufficient number of patients with non-HIE brain injuries and conditions were included in the ICU-ROX trial to confirm or refute an effect of this magnitude.[7] Moreover, an effect of oxygen regimens on outcomes in this subset of patients has not been reported in other recent clinical trials evaluating ICU oxygen regimens.[10,11]

To address the uncertainty, we are conducting Mega-ROX Brains. This trial compares conservative and liberal oxygen therapy regimens in adults with non-HIE acute brain injuries and conditions who are receiving invasive mechanical ventilation in the ICU. Here we present the protocol and statistical analysis plan for Mega-ROX Brains.

2. Methods

2.1. Trial design

Mega-ROX Brains is a three-phase international, multicentre, randomised two-sided superiority trial, designed to test the hypothesis that among adult ICU patients with non-HIE acute brain injuries and conditions who receive unplanned invasive ventilation, liberal oxygen therapy compared to conservative oxygen therapy, reduces in-hospital all-cause mortality up to 90 d from the date of randomisation. It has been designed with reference to the Standard Protocol Items: Recommendations for Interventional Trials checklist.[12] Mega-ROX Brains is one of the three nested trials being conducted within an overall 40,000-participant sample size envelope as a part of the Mega-ROX trial research program. The protocol and statistical analysis plan for the overarching Mega-ROX trial[13] and for the nested Mega-ROX Sepsis have been reported previously.[14] We plan to present data for the non-HIE acute brain injuries and conditions group in a stand-alone manuscript because this nested study has sufficient size to detect a plausible treatment effect. Moreover, given that we are comparing treatment strategies that fall within the spectrum of usual care, we submit that the subgroup data may provide a reasonable basis to individualise oxygen therapy, even if subgroup interaction terms are not statistically significant.[15]

2.2. Setting and population

Mega-ROX Brains 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 aged ≥18 y with non-HIE acute brain injuries and conditions prior to randomisation who receive invasive mechanical ventilation in the ICU following an emergency (unplanned) ICU admission or when mechanical ventilation starts in the ICU (i.e., intubation occurs in the ICU) will be eligible for inclusion. This will include patients with TBI, ischaemic and haemorrhagic stroke, central nervous system infections, autoimmune central nervous system encephalopathies, and SAH. Patients who have seizures in the absence of central

nervous system conditions and with neurological manifestations of non-central nervous system conditions, including those with hepatic encephalopathy or delirium, will not be included.

Patients will be excluded if the enrolment is not considered in their interests by the treating clinician. Operationally, this criterion will exclude all patients where either of the oxygen regimens being tested are considered clinically indicated or contraindicated and those in whom 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.

2.3. 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 the 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. Three randomisation ratios of liberal to conservative oxygen are possible in this trial: (i) 1.05:1 in favour of liberal oxygen therapy; (ii) 1:1.05 in favour of conservative oxygen therapy; and (iii) 1:1. Different randomisation ratios may be used at different times of the 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.[13]

2.4. 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 Brains, liberal oxygen therapy is defined as the *intervention* and will be compared with a *control arm* of conservative oxygen therapy. The details of these approaches have been outlined in the protocol manuscript for the overarching Mega-ROX trial program.[13] In brief, in 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. For participants allocated to the conservative oxygen therapy, the lowest possible FIO_2 to achieve an arterial oxygen saturation on pulse oximetry (SpO_2) level of $\geq$91% will be used. In this group, SpO_2 levels of 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.

The duration of study therapy will be until ICU discharge or 90 d, 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 (nonstudy) 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 to concomitant treatments provided to participants such as the amount of positive end-expiratory pressure used.

2.5. Outcomes

The primary outcome is in-hospital all-cause mortality up to 90 d from the date of randomisation. All participants who survive the index hospital admission and are discharged from that hospital within 90 d 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 90-day all-cause mortality, which will be reported for participants where vital status after hospital discharge can be obtained from registry data source (for example, from a national death registry).

2.6. Data collection and management

Mega-ROX Brains will use a combination of trial-specific data and existing registry data sources. Specific details of data sources that will be used and data management process are reported in the protocol manuscript for the overarching Mega-ROX trial program.[13]

2.7. 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.[13]

2.8. 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 Brains 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 Brains. However, as shown in Fig. 1, an interim analysis specifically for Mega-ROX Brains participants will only occur where there is evidence of heterogeneity of treatment response for participants with versus without acute brain injuries and conditions ($P < 0.05$). If such an analysis is undertaken, stopping rules will be determined by a Haybittle–Peto boundary of $p < 0.001$.

2.9. Sample size and power

The specific sample size of Mega-ROX Brains will be determined by the proportion of participants in the overarching Mega-ROX trial who are identified as having non-HIE acute brain injuries and conditions at baseline. Based on the proportion of participants with these conditions included in the ICU-ROX trial ($\approx$22%),[6] Mega-ROX Brains would be expected to recruit $\approx$9000 participants. Assuming an in-hospital mortality rate of 24.8% in these participants,[6] this sample will provide >90% power to detect an absolute mortality difference of three percentage points (i.e., a reduction to 21.8%) at a

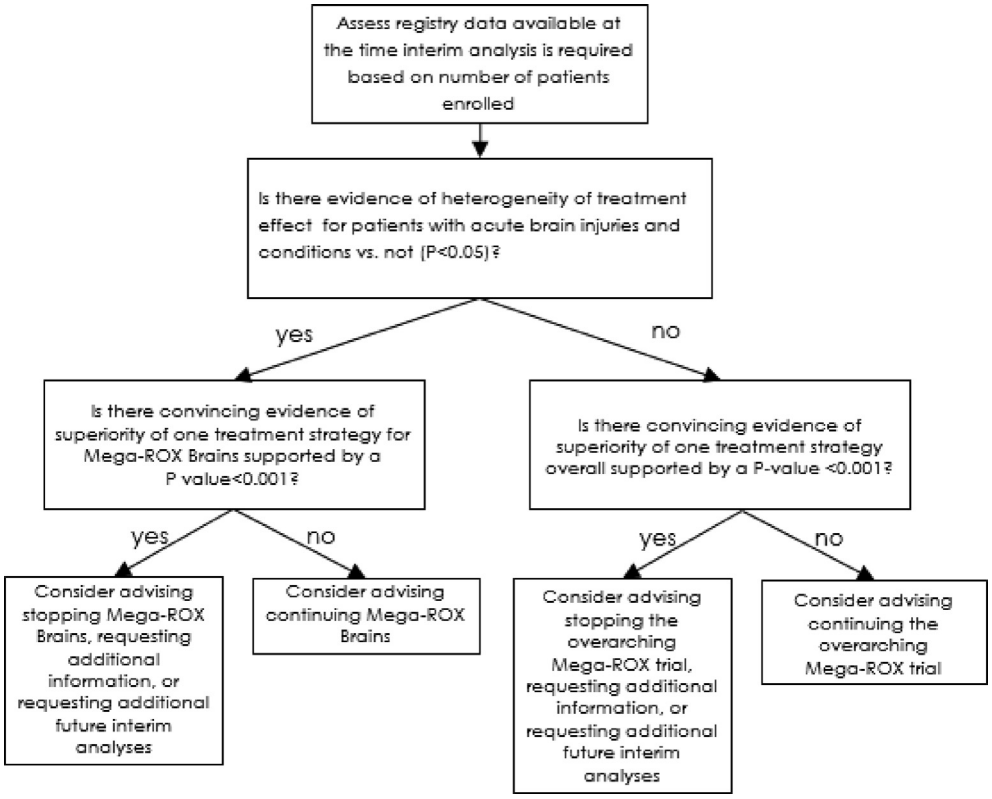

Fig. 1. Overview of steps undertaken by the data monitoring committee at interim analyses, Abbreviations: Mega-ROX: Mega randomised registry trial comparing two approaches to oxygen therapy in the intensive care unit; CNS: central nervous system.

significance level of 0.05. This effect size is much smaller than that of the potential treatment effect suggested by the analysis of participants' non-HIE acute brain injuries and conditions included in the ICU-ROX trial. Around 20% of the first 8226 participants included in the Mega-ROX trial had a non-HIE brain injury or condition, a rate which, if sustained for the rest of the trial, would translate to a Mega-ROX Brains sample of ≈8000 participants. Table 1 summarises a range of potential scenarios for sample size and power for Mega-ROX Brains. We will update the Australian and New Zealand Clinical Trials Registry with the anticipated final sample size, based on the proportion of participants with non-HIE brain injuries and conditions recruited at the time of the fourth interim analysis.

2.10. 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 where consent for 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 by applying a Holm–Bonferroni correction. All analyses will be performed using Stata v17.0 or later (Stata Statistical Software, College Station, TX, USA). Reporting of the study will align with the Consolidated Standard of Reporting Trials (CONSORT) statement.[16]

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

Control event rate[a]	Sample size	Absolute mortality effect (i.e., percentage reduction) detectable with 90% power and a two-sided significance level of 0.05
20%	7500	2.91
20%	8000	2.82
20%	8500	2.74
20%	9000	2.66
20%	9500	2.59
25%	7500	3.17
25%	8000	3.07
25%	8500	2.98
25%	9000	2.90
25%	9500	2.82
30%	7500	3.37
30%	8000	3.27
30%	8500	3.17
30%	9000	3.08
30%	9500	3.00
35%	7500	3.53
35%	8000	3.41
35%	8500	3.31
35%	9000	3.22
35%	9500	3.14
40%	7500	3.64
40%	8000	3.52
40%	8500	3.42
40%	9000	3.32
40%	9500	3.23

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

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 will 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 before final study database lock or 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.

2.10.1. 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 suspected HIE following resuscitation from a cardiac arrest and sepsis. These characteristics will be included in the model because participants with these diagnoses will also be included in the Mega-ROX HIE and Mega-ROX sepsis studies, so there is potential for imbalance in these characteristics across arms of Mega-ROX Brains. 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 and 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 adjustment 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 d) 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 d) 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 the 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 therapy, will be defined as dead and, when assigned to liberal oxygen therapy, will be defined as alive. In the second analysis, these participants, when assigned to conservative oxygen therapy, will be defined as alive and, when assigned to liberal oxygen therapy, will be defined as dead.

2.10.2. 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 subdistribution 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 the treatment group and HIE 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.

Table 2
Mega-ROX Brains baseline characteristics table.

Characteristic	Conservative oxygen therapy (n = xxxx)	Liberal oxygen therapy (n = xxxx)
Age, y	xx.x ± xx	xx.x ± xx
Male sex, no. (%)	xxx (xx.x)	xxx (xx.x)
Body mass index	xx.x ± xx	xx.x ± xx
Clinical frailty score	xxx (xx.x)	xxx (xx.x)
Source of admission to the 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 (excluding transfer from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)
Hours between hospital admission and randomisation	xx.x ± xx	xx.x ± xx
Hours between ICU admission and 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. (%)		
Traumatic brain injury	xxx (xx.x)	xxx (xx.x)
Subarachnoid haemorrhage	xxx (xx.x)	xxx (xx.x)
Intracerebral haemorrhage	xxx (xx.x)	xxx (xx.x)
Ischaemic stroke	xxx (xx.x)	xxx (xx.x)
CNS infection	xxx (xx.x)	xxx (xx.x)
Cerebral venous sinus thrombosis	xxx (xx.x)	xxx (xx.x)
Other	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 ± standard deviation (where the distribution of the data is not approximately symmetric, median [interquartile range] will be reported instead of mean ± standard deviation). 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; SAPS: Simplified Acute Physiology Score; 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.

2.10.3. 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 arterial partial pressure of oxygen (PaO_2) thresholds and those that compared 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.

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% CIs.

2.11. Presentation of outcome data

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

2.12. Subgroup analyses

Given that participants with TBI, SAH, ischaemic stroke, intracerebral haemorrhage, and central nervous system infections were all well represented in ICU-ROX, Mega-ROX Brains should allow for assessment of heterogeneity of treatment effect in these groups. Accordingly, analyses will be performed on four predefined subgroup pairs, irrespective of whether there is evidence of a mortality treatment effect. Heterogeneity between subgroups will be determined by fitting an interaction between treatment and subgroup for the primary outcome (90-day in-hospital mortality). The subgroup pairs will be as follows:

- TBI vs. no TBI.
- SAH vs. no SAH.
- Intracerebral haemorrhage or ischaemic stroke vs. no stroke.
- Central nervous system infection vs. no central nervous system infection.

3. Summary

Mega-ROX Brains is a three-phase international, multicentre, randomised, two-sided superiority trial designed to test the

Table 3
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; FiO_2: fraction of inspired oxygen; SpO_2: arterial oxygen saturation on pulse oximetry; PaO_2: arterial partial pressure of oxygen.

Table 4
Outcomes.

	Conservative oxygen therapy (n = xxxx)	Liberal oxygen therapy (n = xxxx)	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	xxxx	xxxx	
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	xxxx	xxxx	
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	xxxx	xxxx	
Median (IQR)[b]	xx (xx–xx)	xx (xx–xx)	xx (xx to xx)
Discharged home- no. (%)	xxxx (xx.x)	xxxx (xx.x)	**Relative risk** xx (xx to xx) **Risk difference** xx (xx to xx)
90-Day mortality- no. (%)	xxxx (xx.x)	xxxx (xx.x)	**Relative risk** xx (xx to xx) **Risk difference** xx (xx to xx)

Abbreviations: IQR: interquartile range; CI: confidence interval; ICU: intensive care unit.

[a] A P value for the primary outcome comparison will be shown in a footnote. The absolute difference between 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 and ICU and hospital lengths 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 logarithm of time to discharge (or extubation) as the dependent variable. Adjustment will be made for the same variables as for the primary outcome.

hypothesis that among adult ICU participants with non-HIE acute brain pathologies who receive unplanned invasive ventilation, liberal oxygen therapy compared to conservative oxygen therapy, reduces in-hospital all-cause mortality up to 90 d from the date of randomisation. This protocol and the statistical analysis plan article were submitted for publication before the recruitment was completed.

Conflict of interest

None declared.

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Authorship Statement

Young: conceptualisation, methodology, writing - original draft, funding acquisition. **Al-Fares, Aryal, Arabi, Ashraf, Basri Mat-Nor, Borghi, de Oliveira Manoelo, Fujii, Hodgson, Mangal, Nichol, Tomazini:** 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.04.011.

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