Proposed presentation of data for Mega-ROX.

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Mega-ROX is endorsed by the Australian and New Zealand Clinical Trials Group, the Critical Care Asia and Africa Network, the Irish Critical Care-Clinical Trials Group, and the Alberta Health Services Critical Care Strategic Clinical Network.

TABLES

Table 1: Baseline characteristics*

Characteristic	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Body mass index	xx.x ± xx	xx.x ± xx
Clinical frailty score	x ± x	x ± x
Source of admission to ICU – no. (%)		
Emergency department	xxxx (xx.x)	xxxx (xx.x)
Hospital ward	xxxx (xx.x)	xxxx (xx.x)
Transfer from another ICU	xxxx (xx.x)	xxxx (xx.x)
Transfer from another hospital (except from another ICU)	xxxx (xx.x)	xxxx (xx.x)
From OT following surgery	xxxx (xx.x)	xxxx (xx.x)
Subgroup diagnoses– no. (%)		
Confirmed or suspected hypoxic ischaemic encephalopathy	xxxx (xx.x)	xxxx (xx.x)
Confirmed or strongly suspected sepsis	xxxx (xx.x)	xxxx (xx.x)
Acute brain pathology other than hypoxic ischaemic encephalopathy	xxxx (xx.x)	xxxx (xx.x)
COVID-19 disease	xxxx (xx.x)	xxxx (xx.x)
Enrolled in a low or middle income country	xxxx (xx.x)	xxxx (xx.x)
ICU admission to randomisation less than 2 hours	xxxx (xx.x)	xxxx (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*	xx.x ± xx	xx.x ± xx
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 symmetric, 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.
* Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
Abbreviations: APACHE: Acute Physiology And Chronic Health Evaluation; 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.

Table 2: Oxygen exposure by treatment group

Oxygen exposure metric – n (%)	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)	Between-Group difference (95% CI)
Proportion of hours SpO_2 ≥97%	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Number of hours SpO_2 ≥97%	xx (xx.x)	xx (xx.x)	xx (xx to xx)
Proportion of hours SpO_2 <88%	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Number of hours SpO_2 <88%	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Proportion of patients with at least one PaO_2 recording <60mmHg	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Proportion of patients with at least one PaO_2 recording >100mmHg	xx (xx.x)	xx (xx.x)	xx (xx to xx)
Proportion of hours FIO_2 0.21	xx (xx.x)	xx (xx.x)	xx (xx to xx)
Number of hours FIO_2 0.21	xx (xx.x)	xx (xx.x)	xx (xx to xx)

Abbreviations: IQR: Interquartile range; CI: Confidence Interval

Table 3: Outcomes

	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)	Estimate (95% CI)
Primary outcome*			
Died at the hospital by day 90- no. (%)	xxxx (xx.x)	xxxx (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‡**
Number of patients	xxxxx	xxxxx	
Median (IQR)†	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Days until discharged alive from ICU			**Subhazard ratio of time to ICU discharge‡**
Number of patients	xxxxx	xxxxx	
Median (IQR)†	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Days until discharged alive from hospital			**Subhazard ratio of time to Hospital discharge‡**
Number of patients	xxxxx	xxxxx	
Median (IQR)†	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Discharged home- no. (%)	xxxxx (xx.x)	xxxxx (xx.x)	**Relative risk** xx (xx to xx) **Risk difference** xx (xx to xx)
Day-90 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

* 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 adjusting 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, sepsis, and acute brain pathologies other than hypoxic ischaemic encephalopathy.

† Duration of invasive mechanical ventilation and ICU and hospital length of stay will be calculated from cumulative incidence functions with mortality regarded as a competing risk.

‡ 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.

SUPPLEMENTAL TABLES

Table S1: Study data sources in each country/region (data shown here are indicative as some regions have not yet commenced recruitment/data collection.

	ANZ	Canada	Ireland	Japan	Kuwait	Malaysia	Namibia	Nepal	Pakistan	Saudi Arabia
Baseline data										
Age*	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Sex at birth*	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
ICU admission date*	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Hospital admission date*	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
ICU admission source†	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗
ICU admission type‡	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗
APACHE-II score	✓	✓	✓	✓	✗	✗	✓	✓	✓	✗
Outcome data					✗					
In-hospital mortality during index hospitalisation within 90 days (primary end point)	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Date of death (if died during index hospitalisation within 90 days)	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Date of ICU discharge* (used to calculate ICU length of stay)	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Date of hospital discharge (used to calculate hospital length of stay)	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Hospital discharge destination¶	✓	✓	✓	✓	✗	✗	✓	✓	✓	✗
Duration of invasive mechanical ventilation	✗	✓	✓	✓	✗	✓	✓	✓	✓	✗
Mortality within 90 days of randomisation¥	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Date of death within 90 days of randomisation¥	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

Abbreviations: ANZ: Australia and New Zealand; APACHE-II: Acute Physiology and Chronic Health Evaluation II; ICU: intensive care unit
* These data will also be collected via the study randomisation interface so that these fields (along with site of randomisation) can be used to verify that registry data provided are correctly assigned to the appropriate patient in the study database.
† ICU admission source will be categorised as ED, operating theatre/recovery, ward, other hospital (not ICU), other ICU.
‡ICU admission type will categorised as elective surgical, emergency surgical, or non-surgical/medical
§ Data will be provided from individual sites where they are available.
¶ Hospital discharge destination will be categorised as died, home, other medical care facilities, and other.
¥ Including where the patient dies following hospital discharge.
In Kuwait, data will not be obtained from a registry but will instead be collected from individual patient medical records using a case report form.

Table S2: Additional baseline variables – body system & anatomical site		
Body system and anatomical site involved – no. (%)	**Conservative oxygen therapy (n=xxxxx)**	**Liberal oxygen therapy (n=xxxxx)**
Respiratory system	xxx (xx.x)	xxx (xx.x)
Upper airway or trachea	xxx (xx.x)	xxx (xx.x)
Bronchi or lower airways	xxx (xx.x)	xxx (xx.x)
Pulmonary vasculature	xxx (xx.x)	xxx (xx.x)
Lungs	xxx (xx.x)	xxx (xx.x)
Pleura or mediastinum	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Coronary arteries	xxx (xx.x)	xxx (xx.x)
Myocardium or cardiac chambers	xxx (xx.x)	xxx (xx.x)
Pericardium, pericardial space or mediastinum	xxx (xx.x)	xxx (xx.x)
Heart valves	xxx (xx.x)	xxx (xx.x)
Conducting system or rhythm disturbances	xxx (xx.x)	xxx (xx.x)
Thoracic aorta	xxx (xx.x)	xxx (xx.x)
Splanchnic or renal vessels	xxx (xx.x)	xxx (xx.x)
Neck or extracranial vessels	xxx (xx.x)	xxx (xx.x)
Limb or limb girdle vessels	xxx (xx.x)	xxx (xx.x)
Great veins	xxx (xx.x)	xxx (xx.x)
Peripheral vasculature, shock or hypertension	xxx (xx.x)	xxx (xx.x)
Pulmonary vasculature	xxx (xx.x)	xxx (xx.x)
Uterine or ovarian vessels	xxx (xx.x)	xxx (xx.x)
Abdominal aorta	xxx (xx.x)	xxx (xx.x)
Iliac vessels	xxx (xx.x)	xxx (xx.x)
Gastrointestinal system		
Mouth or pharynx	xxx (xx.x)	xxx (xx.x)
Oesophagus	xxx (xx.x)	xxx (xx.x)
Stomach	xxx (xx.x)	xxx (xx.x)
Duodenum	xxx (xx.x)	xxx (xx.x)
Small bowel	xxx (xx.x)	xxx (xx.x)
Large bowel, rectum or anus	xxx (xx.x)	xxx (xx.x)
Liver or biliary tree	xxx (xx.x)	xxx (xx.x)
Spleen	xxx (xx.x)	xxx (xx.x)
Pancreas	xxx (xx.x)	xxx (xx.x)
Abdominal wall or peritoneum	xxx (xx.x)	xxx (xx.x)
Neurological system		
Head (extracranial), neck or eyes	xxx (xx.x)	xxx (xx.x)
Brain, CSF, meninges or skull vault	xxx (xx.x)	xxx (xx.x)
Spinal cord	xxx (xx.x)	xxx (xx.x)
Peripheral nervous system	xxx (xx.x)	xxx (xx.x)
Neuro-muscular junction	xxx (xx.x)	xxx (xx.x)
Genito-urinary system		
Kidney or ureter	xxx (xx.x)	xxx (xx.x)
Bladder or urethra	xxx (xx.x)	xxx (xx.x)
Ovary, fallopian tubes, uterus or genitalia (non-obstetric)	xxx (xx.x)	xxx (xx.x)
Ovary, fallopian tubes, uterus or genitalia (obstetric)	xxx (xx.x)	xxx (xx.x)
Testes, prostate or penis	xxx (xx.x)	xxx (xx.x)

Table S2 continued: Additional baseline variables – body system & anatomical site		
Endocrine, metabolic, thermoregulatory, and poisoning		
Thyroid	xxx (xx.x)	xxx (xx.x)
Adrenal	xxx (xx.x)	xxx (xx.x)
Endocrine pancreas	xxx (xx.x)	xxx (xx.x)
Parathryoids	xxx (xx.x)	xxx (xx.x)
Ovaries	xxx (xx.x)	xxx (xx.x)
Thermoregulation	xxx (xx.x)	xxx (xx.x)
Body fluids or tissues	xxx (xx.x)	xxx (xx.x)
Body composition	xxx (xx.x)	xxx (xx.x)
Chromosomal abnormalities	xxx (xx.x)	xxx (xx.x)
Poisoning	xxx (xx.x)	xxx (xx.x)
Haematological / immunological		
Blood	xxx (xx.x)	xxx (xx.x)
Bone marrow	xxx (xx.x)	xxx (xx.x)
Musculoskeletal and skin		
Vertebral column	xxx (xx.x)	xxx (xx.x)
Pelvis, long bones, or joints	xxx (xx.x)	xxx (xx.x)
Muscles or connective tissue	xxx (xx.x)	xxx (xx.x)
Skin	xxx (xx.x)	xxx (xx.x)
Psychiatric	xxx (xx.x)	xxx (xx.x)

Table S3: Additional baseline variables - comorbid conditions		
	Conservative oxygen therapy (n=xxxxx)	**Liberal oxygen therapy (n=xxxxx)**
Co-morbid conditions – no. (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Hepatic	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Immunosuppression by disease	xxx (xx.x)	xxx (xx.x)
Immunosuppression by therapy	xxx (xx.x)	xxx (xx.x)

Table S4: Additional baseline variables - additional details on nested-trial subgroups, surgical admissions, key pathological processes leading to ICU admission*

	Conservative oxygen therapy (n=xxxxx)	**Liberal oxygen therapy (n=xxxxx)**
Overlap of subgroups– n (%)		
Confirmed or suspected hypoxic ischaemic encephalopathy alone	xxxx (xx.x)	xxxx (xx.x)
Confirmed or strongly suspected sepsis alone	xxxx (xx.x)	xxxx (xx.x)
Acute brain pathology other than hypoxic ischaemic encephalopathy only	xxxx (xx.x)	xxxx (xx.x)
Confirmed or suspected hypoxic ischaemic encephalopathy AND confirmed or strong suspected sepsis	xxxx (xx.x)	xxxx (xx.x)
Confirmed or suspected hypoxic ischaemic encephalopathy AND acute brain pathology other than hypoxic ischaemic encephalopathy	xxxx (xx.x)	xxxx (xx.x)
Acute brain pathology other than hypoxic ischaemic encephalopathy AND confirmed or strongly suspected sepsis	xxxx (xx.x)	xxxx (xx.x)
Confirmed or suspected hypoxic ischaemic encephalopathy AND confirmed or strong suspected sepsis AND acute brain pathology other than hypoxic ischaemic encephalopathy	xxxx (xx.x)	xxxx (xx.x)
Surgical admission details– n (%)		
Admitted to ICU from OT following elective surgery	xxxx (xx.x)	xxxx (xx.x)
Admitted to ICU from OT following emergency surgery	xxxx (xx.x)	xxxx (xx.x)
Pathological processes– n (%)		
Coma / encephalopathy	xxx (xx.x)	xxx (xx.x)
Infection	xxx (xx.x)	xxx (xx.x)
Inflammation	xxx (xx.x)	xxx (xx.x)
Haemorrhage	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Tumour or malignancy	xxx (xx.x)	xxx (xx.x)

* The top 10 process categories will be listed; examples are shown in mock table above.

Table S5: Additional information of duration and length of stay outcomes

	Conservative oxygen therapy (n=xxxxx)	Liberal oxygen therapy (n=xxxxx)	Ratio (95% CI)
Duration of invasive mechanical ventilation (hours) – geometric mean (95% CI)			
Survivors	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Non-survivors	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
ICU length of stay (days) – geometric mean (95% CI)			
Survivors	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Non-survivors	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Hospital length of stay (days) – geometric mean (95% CI)			
Survivors	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)
Non-survivors	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)

Table S6: Additional details on separation in oxygen exposure*

Variable	Conservative oxygen therapy (n=xxxxx)	Standard oxygen therapy (n=xxxxx)	Odds ratio or estimate of difference† (95% CI)	P value
Hours SpO_2 ≥97%				
			odds ratio (95% CI)	
Proportion of hours per patient SpO_2 ≥97% n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)	x.xx
			difference in medians† (95% CI)	
Median [IQR] proportion of hours per patient SpO_2 ≥97%	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)	x.xx
Median [IQR] number of hours per patient SpO_2 ≥97%	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)	x.xx
Hours SpO_2 <91%				
			odds ratio (95% CI)	
Proportion of hours per patient SpO_2 <91% n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)	x.xx
			difference in medians† (95% CI)	
Median [IQR] proportion of hours per patient SpO_2 <91%	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)	x.xx
Median [IQR] number of hours per patient SpO_2 <91%	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)	x.xx
Hours SpO_2 <88%				
			odds ratio (95% CI)	
Proportion of hours per patient SpO_2 <88% n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)	x.xx
			difference in medians† (95% CI)	
median [IQR] proportion of hours per patient SpO_2 <88%	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)	x.xx
median [IQR] number of hours per patient SpO_2 <88%	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)	x.xx
Hours FiO_2 0.21				
			odds ratio (95% CI)	
Proportion of hours per patient with an FiO_2 of 0.21 n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)	x.xx
			difference in medians† (95% CI)	
median [IQR] proportion of hours per patient with an FiO_2 of 0.21	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)	x.xx
median [IQR] number of hours per patient with an FiO_2 of 0.21	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)	x.xx

* SpO_2 hours above and below specified thresholds and hours on an FiO_2 of 0.21 were obtained from all values recorded on the ICU flow chart (up to a maximum of one value per hour) up until day 10 post randomisation including after extubation even where supplemental oxygen therapy was not being administered.
† Differences will be calculated using quantile regression incorporating adjusting 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, sepsis, and acute brain pathologies other than hypoxic ischaemic encephalopathy.
Abbreviations: CI: confidence interval; FiO_2: Fraction of inspired oxygen; IQR: Interquartile range; SpO2: Arterial oxygen saturation measure by peripheral pulse oximetry

FIGURES:

Figure 1: Participant flow diagram

Description: Participant flow diagram.

Figure 2A: Kaplan-Meier survival estimates of the probably of survival to day 90

Description: Line graph with days 0 to 90 on the horizontal axis and probability of survival on the vertical axis.

Figure 2B: Forest plot for subgroup treatment effects on mortality

SUPPLEMENTAL FIGURES:

Figure S1A: Mean FiO_2 by treatment group

Description: Line graph with days 0 to 10 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 patient is invasively ventilated in the ICU up until day 10. Data points will be reported with corresponding standard error bars.

Figure S1B: Highest FiO_2 by treatment group

Description: Line graph with days 0 to 10 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. Highest FiO_2 will be recorded daily while the patient is invasively ventilated in ICU up until day 10. Data points will be reported with corresponding standard error bars.

Figure S1C: Lowest FiO_2 by treatment group

Description: Line graph with days 0 to 10 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. Lowest FiO_2 will be recorded daily while the patient is invasively ventilated in ICU up until day 28. Data points will be reported with corresponding standard error bars.

Figure S2A: Mean daily PaO_2 by treatment group

Description: Line graph with days 0 to 10 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 patient is in the ICU up until day 10. Data points will be reported with corresponding standard error bars.

Figure S2B: Highest daily PaO_2 by treatment group

Description: Line graph with days 0 to 10 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. Highest PaO_2 will be recorded daily while the patient is in ICU up until day 28. Data points will be reported with corresponding standard error bars.

Figure S2C: Lowest PaO_2 by treatment group

Description: Line graph with days 0 to 10 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. Lowest PaO_2 will be recorded daily while the patient is in ICU up until day 28. Data points will be reported with corresponding standard error bars.