

## **Proposed presentation of data for ICU-ROX.**

Version 1 was posted online on 21 November 2017 (prior to the interim analysis which occurred when the 500<sup>th</sup> participant reached day 28).

Version 2 was posted online on 15 May 2018 (prior to completion of recruitment).

Version 3 was posted online on 17 September 2018 (prior to completion of follow-up or database lock)

Version 4 was posted online on 11 December 2018 (after database lock but prior to analyses being undertaken)

Version 5 was posted online on 13<sup>th</sup> of February 2019 (during analyses)

The ICU-ROX management committee members are Paul J Young (Chair), Diane M Mackle, Richard W Beasley, Victoria L Bennett, Adam M Deane, Glenn M Eastwood, Simon Finfer, Ross C Freebairn, Edward Litton, Natalie J Linke, Colin J McArthur, Shay P McGuinness, Rakshit Panwar, and Rinaldo Bellomo.

ICU-ROX is endorsed by the ANZICS-CTG.

### **SUMMARY OF CHANGES FROM PREVIOUS VERSION**

#### Changes between version 1 and version 2

1. Non-invasive baseline supports have been removed from Table S2 because inclusion in the trial requires that the patient is invasively ventilated. Thus, at the time of randomization patients cannot be receiving non-invasive modes.

#### Changes between version 2 and version 3

1. Because of concerns about the overuse of p-values and significance tests in the medical literature, results other than the principal analysis of the primary end point will, except as specified, now only be summarised with point estimates for differences between groups (or rate ratios) and 95% confidence intervals for those differences. The tables outlining the proposed presentation of data have been updated accordingly.

#### Changes between version 3 and version 4

1. The order of the Tables and Figures has been amended to reflect the order we propose presenting these in the final manuscript.  
2. Vasopressor-free days have been added to Table S9 because this process of care measure was inadvertently omitted previously.

#### Changes between version 4 and version 5

1. The labels and descriptions of FigS4A and FigS5 have been amended because, as outlined in the published SAP, we plan to present PaO<sub>2</sub> and PaCO<sub>2</sub> data using time-weighted means rather than means. The previous labelling had erroneously indicated that we would present means.

## TABLES

<b>Table 1: Baseline characteristics*</b>		
<b>Characteristic</b>	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
<b>Co-morbid conditions – no. (%)</b>		
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)
Metastatic Cancer	xxx (xx.x)	xxx (xx.x)
<b>Source of admission to ICU – no. (%)</b>		
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)
Hours from initiation of invasive ventilation 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
<b>Physiology</b>		
Respiratory rate – breaths per minute	xx.x ± xx	xx.x ± xx
SpO <sub>2</sub> - %	xx.x ± xx	xx.x ± xx
PaO <sub>2</sub> – mmHg	xx.x ± xx	xx.x ± xx
PaO <sub>2</sub> /FiO <sub>2</sub> ratio – mmHg	xx.x ± xx	xx.x ± xx
PaCO <sub>2</sub> – mmHg	xx.x ± xx	xx.x ± xx
<b>Physiological support</b>		
FiO <sub>2</sub>	xx.x ± xx	xx.x ± xx
PEEP – cmH <sub>2</sub> O	xx.x ± xx	xx.x ± xx
Inotrope / vasopressor support – no. (%)	xxx (xx.x)	xxx (xx.x)
Renal replacement therapy – no. (%)	xxx (xx.x)	xxx (xx.x)

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, 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.

\* Statistically significant differences in baseline characteristics between groups will be indicated by \* for P < 0.05, \*\* for P < 0.01, and \*\*\* for P < 0.001.

† 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<sub>2</sub>: arterial oxygen saturation on pulse oximetry; PaO<sub>2</sub>: arterial partial pressure of oxygen; FiO<sub>2</sub>: fraction of inspired oxygen; PaCO<sub>2</sub>: arterial partial pressure of carbon dioxide; PEEP: positive end expiratory pressure.

<b>Table 2: Primary outcome and key secondary outcomes</b>				
	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>	<b>Estimate (95% CI)</b>	
<b>Primary outcome</b>				
			<b>difference in medians*; P value†</b>	
Ventilator-free days – median (IQR)	xx (xx-xx)	xx (xx-xx)	xx (xx to xx); x.xx	
			<b>mean difference</b>	
Ventilator-free days – mean ± SD	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
			<b>ratio of geometric means</b>	
Days of ventilation (survivors only) - geometric mean (95% CI)	xx (xx-xx)	xx (xx-xx)	(xx to xx)	
<b>Key secondary outcomes – no. (%)</b>			<b>odds ratio</b>	
			<b>unadjusted</b>	<b>adjusted‡</b>
Day 90 mortality	xx (xx.x)	xx (xx.x)	xx (xx-xx)	xx (xx-xx)
Day 180 mortality	xx (xx.x)	xx (xx.x)	xx (xx-xx)	xx (xx-xx)

\* Hodges-Lehmann estimate of absolute difference for conservative oxygen minus standard oxygen therapy. The Hodges-Lehmann estimate is the median of all paired differences between observations in the two samples.

† A p-value will be presented for the principal analysis of the primary end point only.

‡ Adjusted for age, gender, and APACHE-II score as well as for any observed baseline differences P value ≤0.1 with patients nested in site and site treated as a random variable.

Abbreviations: IQR: Interquartile range; CI: Confidence Interval

## SUPPLEMENTAL TABLES

**Table S1:** Changes to study methodology between the internal pilot phase and the main study

<b>Table S2: Characteristics of internal pilot vs. main study patients*</b>		
<b>Characteristic</b>	<b>Internal pilot (n=xxx)</b>	<b>Main study (n=xxx)</b>
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
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)
Metastatic Cancer	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 elective surgery	xxx (xx.x)	xxx (xx.x)
From OT following emergency surgery	xxx (xx.x)	xxx (xx.x)
Hours from initiation of invasive ventilation 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
Physiology		
Respiratory rate – breaths per minute	xx.x ± xx	xx.x ± xx
SpO <sub>2</sub> – %	xx.x ± xx	xx.x ± xx
PaO <sub>2</sub> – mmHg	xx.x ± xx	xx.x ± xx
PaO <sub>2</sub> /FiO <sub>2</sub> ratio – mmHg	xx.x ± xx	xx.x ± xx
PaCO <sub>2</sub> – mmHg	xx.x ± xx	xx.x ± xx
Physiological support		
FiO <sub>2</sub>	xx.x ± xx	xx.x ± xx
PEEP – cmH <sub>2</sub> O	xx.x ± xx	xx.x ± xx
Inotrope / vasopressor support – no. (%)	xxx (xx.x)	xxx (xx.x)
Renal replacement therapy – no. (%)	xxx (xx.x)	xxx (xx.x)
Length of stay – days (median [IQR])		
ICU length of stay	xx [xx-xx]	xx [xx-xx]
Hospital length of stay	xx [xx-xx]	xx [xx-xx]
Ventilator-free days	xx [xx-xx]	xx [xx-xx]
Day 90 mortality	xxx (xx.x)	xxx (xx.x)
Day 180 mortality	xxx (xx.x)	xxx (xx.x)

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, median [IQR] will be reported instead of mean ± SD).

\* Statistically significant differences between groups will be indicated by \* for P < 0.05, \*\* for P < 0.01, and \*\*\* for P < 0.001.

† 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<sub>2</sub>: arterial oxygen saturation on pulse oximetry; PaO<sub>2</sub>: arterial partial pressure of oxygen; FiO<sub>2</sub>: fraction of inspired oxygen; OT: operating theatre; PaCO<sub>2</sub>: arterial partial pressure of carbon dioxide; PEEP: positive end expiratory pressure.

<b>Table S3: Characteristics of enrolled vs. missed patients*</b>		
<b>Characteristic</b>	<b>Enrolled patients (n=xxx)</b>	<b>Missed patients† (n=xxx)</b>
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Illness severity – % risk of death		
ANZ ROD	xx.x ± xx	xx.x ± xx
ANZ ROD (no oxygen)‡	xx.x ± xx	xx.x ± xx
APACHE-III ROD	xx.x ± xx	xx.x ± xx
Major APACHE-III diagnostic groups		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Musculoskeletal	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Other	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 hospital	xxx (xx.x)	xxx (xx.x)
Operating theatre	xxx (xx.x)	xxx (xx.x)
Length of stay – days (median [IQR])		
ICU length of stay	xx [xx-xx]	xx [xx-xx]
Hospital length of stay	xx [xx-xx]	xx [xx-xx]
In-hospital mortality – no. (%)	xxx (xx.x)	xxx (xx.x)

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, median [IQR] will be reported instead of mean ± SD).

\* Statistically significant differences between groups will be indicated by \* for P < 0.05, \*\* for P < 0.01, and \*\*\* for P < 0.001.

† Enrolment will be restricted to patients who have received less than two hours of invasive mechanical ventilation and/or non-invasive ventilation in an ICU. Patients who fulfill all other eligibility but are not enrolled within the two hour time window will be categorised as 'missed'.

‡ The ANZ ROD was calculated with the oxygen component removed

Abbreviations: ANZ: Australia and New Zealand; APACHE: Acute Physiology And Chronic Health Evaluation; ICU: Intensive Care Unit; ROD: risk of death.

<b>Table S4: Additional baseline characteristics*</b>		
<b>Characteristic</b>	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>
Ethnicity† – no. (%)		
Asian	xxx (xx.x)	xxx (xx.x)
European	xxx (xx.x)	xxx (xx.x)
Maori	xxx (xx.x)	xxx (xx.x)
Pacific Island Peoples	xxx (xx.x)	xxx (xx.x)
Middle Eastern / Latin / African	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)

Employment status at baseline	<b>(n=xxx)</b>	<b>(n=xxx)</b>
Working full time	xxx (xx.x)	xxx (xx.x)
Working part time	xxx (xx.x)	xxx (xx.x)
On leave but still employed	xxx (xx.x)	xxx (xx.x)
Temporarily laid off	xxx (xx.x)	xxx (xx.x)
Unemployed but looking for work	xxx (xx.x)	xxx (xx.x)
Wanting to work but unemployed due to health	xxx (xx.x)	xxx (xx.x)
Unemployed and not part of any category	xxx (xx.x)	xxx (xx.x)
Keeping house or being a home maker	xxx (xx.x)	xxx (xx.x)
Retired	xxx (xx.x)	xxx (xx.x)
Receiving disability	xxx (xx.x)	xxx (xx.x)
Studying	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)
Cognitive function	<b>(n=xxx)</b>	<b>(n=xxx)</b>
IQCODE‡	xxx (xx.x)	xxx (xx.x)
Operative category	<b>(n=xxx)</b>	<b>(n=xxx)</b>
Non-operative	xxx (xx.x)	xxx (xx.x)
Operative (elective)	xxx (xx.x)	xxx (xx.x)
Operative (emergency)	xxx (xx.x)	xxx (xx.x)
Baseline physiology / support	<b>(n=xxx)</b>	<b>(n=xxx)</b>
Body temperature – °C	xx.x ± xx	xx.x ± xx
Heart rate – beats per minute	xx.x ± xx	xx.x ± xx
Serum creatinine – µmol/L	xx.x ± xx	xx.x ± xx
Mean arterial pressure - mmHg	xx.x ± xx	xx.x ± xx
Mean airway pressure – cmH <sub>2</sub> O	xx.x ± xx	xx.x ± xx
Therapies at randomisation	<b>(n=xxx)</b>	<b>(n=xxx)</b>
Tracheostomy	xxx (xx.x)	xxx (xx.x)
ECMO/ECCO <sub>2</sub> R	xxx (xx.x)	xxx (xx.x)
Ongoing neuromuscular blockade	xxx (xx.x)	xxx (xx.x)
Nitric oxide	xxx (xx.x)	xxx (xx.x)
Prone positioning	xxx (xx.x)	xxx (xx.x)
Prostaglandins	xxx (xx.x)	xxx (xx.x)

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, 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.

\* Statistically significant differences in baseline characteristics between groups will be indicated by \* for P < 0.05, \*\* for P < 0.01, and \*\*\* for P < 0.001.

† Ethnicity data were only collected for participants enrolled in New Zealand.

‡ The IQCODE measures the impression of a relative or friend of the patient's present performance compared with 10 years ago: 1=much improved; 2=a bit improved; 3=not much change; 4=a bit worse; 5=much worse

Abbreviations: ECMO: extracorporeal membrane oxygenation; ECCO<sub>2</sub>R: extracorporeal carbon dioxide removal; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly.

**Table S5: Baseline respiratory support**

Ventilation modes – n (%)	Conservative oxygen therapy (n=XXX)	Standard oxygen therapy (N=XXX)
Invasive ventilation modes		
Assist control volume mode	xxx (xx.x)	xxx (xx.x)
Assist control pressure mode	xxx (xx.x)	xxx (xx.x)
Synchronised intermittent mandatory ventilation volume control	xxx (xx.x)	xxx (xx.x)
Synchronised intermittent mandatory ventilation pressure control	xxx (xx.x)	xxx (xx.x)
Pressure support	xxx (xx.x)	xxx (xx.x)
Pressure control	xxx (xx.x)	xxx (xx.x)

Airway pressure release ventilation	xxx (xx.x)	xxx (xx.x)
Pressure regulated volume control	xxx (xx.x)	xxx (xx.x)
High frequency oscillatory ventilation	xxx (xx.x)	xxx (xx.x)
Adaptive Support Ventilation	xxx (xx.x)	xxx (xx.x)
Other Invasive mode	xxx (xx.x)	xxx (xx.x)

**Table S6:** Intensive Care Admission Diagnoses

<b>Diagnostic category</b>	<b>Conservative oxygen therapy (n=XXX)</b>	<b>Standard oxygen therapy (N=XXX)</b>
<b>Operative admission diagnosis – n (%)</b>		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Gynaecological	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Metabolic	xxx (xx.x)	xxx (xx.x)
Musculoskeletal / skin	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
<b>Non-operative admission diagnosis – n (%)</b>		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Gynaecological	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Metabolic	xxx (xx.x)	xxx (xx.x)
Musculoskeletal / skin		
Neurological	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)

**Table S7:** Details of acute brain pathologies at baseline

<b>Category – n (%)</b>	<b>Conservative oxygen therapy (n=XXX)</b>	<b>Standard oxygen therapy (N=XXX)</b>
Traumatic brain injury	xxx (xx.x)	xxx (xx.x)
Hypoxic ischaemic encephalopathy	xxx (xx.x)	xxx (xx.x)
Ischaemic stroke	xxx (xx.x)	xxx (xx.x)
CNS infection	xxx (xx.x)	xxx (xx.x)
Haemorrhagic stroke	xxx (xx.x)	xxx (xx.x)
Subarachnoid haemorrhage	xxx (xx.x)	xxx (xx.x)
Other acute brain pathology	xxx (xx.x)	xxx (xx.x)

Abbreviations: CNS: central nervous system

<b>Table S8: Separation in oxygen exposure*</b>			
<b>Variable</b>	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>	<b>Odds ratio or estimate of difference† (95% CI)</b>
<b>Hours SpO<sub>2</sub> ≥97%</b>			
			<b>odds ratio (95% CI)</b>
Proportion of hours per patient SpO <sub>2</sub> ≥97% n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)
			<b>difference in medians† (95% CI)</b>
Median [IQR] proportion of hours per patient SpO <sub>2</sub> ≥97%	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)
Median [IQR] number of hours per patient SpO <sub>2</sub> ≥97%	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)
<b>Hours SpO<sub>2</sub> &lt;91%</b>			
			<b>odds ratio (95% CI)</b>
Proportion of hours per patient SpO <sub>2</sub> <91% n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)
			<b>difference in medians† (95% CI)</b>
Median [IQR] proportion of hours per patient SpO <sub>2</sub> <91%	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)
Median [IQR] number of hours per patient SpO <sub>2</sub> <91%	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)
<b>Hours SpO<sub>2</sub> &lt;88%</b>			
			<b>odds ratio (95% CI)</b>
Proportion of hours per patient SpO <sub>2</sub> <88% n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)
			<b>difference in medians† (95% CI)</b>
median [IQR] proportion of hours per patient SpO <sub>2</sub> <88%	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)
median [IQR] number of hours per patient SpO <sub>2</sub> <88%	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)
<b>Hours FiO<sub>2</sub> 0.21</b>			
			<b>odds ratio (95% CI)</b>
Proportion of hours per patient with an FiO <sub>2</sub> of 0.21 n/N (%)	xx/xx (xx)	xx/xx (xx)	xx (xx to xx)
			<b>difference in medians† (95% CI)</b>
median [IQR] proportion of hours per patient with an FiO <sub>2</sub> of 0.21	x.xx [x.xx-x.xx]	x.xx [x.xx-x.xx]	xx (xx to xx)
median [IQR] number of hours per patient with an FiO <sub>2</sub> of 0.21	x.x [x.x-x.x]	x.x [x.x-x.x]	xx (xx to xx)

\* SpO<sub>2</sub> hours above and below specified thresholds and hours on an FiO<sub>2</sub> 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 28 post randomisation including after extubation even where supplemental oxygen therapy was not being administered.

† Hodges-Lehmann estimate of absolute difference for conservative oxygen minus standard oxygen therapy. The Hodges-Lehmann estimate is the median of all paired differences between observations in the two samples.

Abbreviations: CI: confidence interval; FiO<sub>2</sub>: Fraction of inspired oxygen; IQR: Interquartile range; SpO<sub>2</sub>: Arterial oxygen saturation measure by peripheral pulse oximetry



**Table S9:** Additional physiological descriptors and process of care measures in ICU

Variable	Conservative oxygen therapy	Standard oxygen therapy	Ratio or estimate of difference
	(n=xxx)	(n=xxx)	odds ratio (95% CI)
Proportion of patients who received renal replacement therapy in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received a tracheostomy in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received extracorporeal membrane oxygenation or CO <sub>2</sub> removal in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received neuromuscular blockers by infusion in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received nitric oxide in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received prone positioning in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received prostaglandins in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Proportion of patients who received a red cell transfusion in the ICU* – no. (%)	xxx (xx.x)	xxx (xx.x)	xx (xx to xx)
Number of units transfused among patients who received a red cell transfusion	xx ± xx	xx ± xx	
			<b>mean difference (95% CI)</b>
Delta serum creatinine† - µmol/L (95% CI)	xx (xx to xx)	xx (xx to xx)	xx (xx to xx)
Number of arterial blood gases performed per patient in the first 10 days in ICU	xx ± xx	xx ± xx	xx (xx to xx)
			<b>difference in medians ‡ (95% CI)</b>
Hours from randomisation to ICU discharge§	x.x [x.x to x.x]	x.x [x.x to x.x]	x.xx
Hours from randomisation to hospital discharge§	x.x [x.x to x.x]	x.x [x.x to x.x]	x.xx
Vasopressor free days	x.x [x.x to x.x]	x.x [x.x to x.x]	x.xx

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, median [IQR] will be reported instead of mean ± SD). Values followed by square brackets will be median [IQR]

\* Proportion who received RRT and proportion who received a tracheostomy censored at day 28; others censored at day 10

† Difference between the most recent pre-enrollment serum creatinine level and the peak serum creatinine level measured in ICU up until day 28.

‡ Hodges-Lehmann estimate of absolute difference for conservative oxygen minus standard oxygen therapy. The Hodges-Lehmann estimate is the median of all paired differences between observations in the two samples.

§ Censored at day 90

<b>Table S10: Cause-specific mortality at day 180 by treatment group</b>		
	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>
<b>Cardiovascular</b>		
Arrhythmia	xxx (xx.x)	xxx (xx.x)
Cardiogenic shock	xxx (xx.x)	xxx (xx.x)
Distribute (Septic) shock	xxx (xx.x)	xxx (xx.x)
Hypovolaemic shock	xxx (xx.x)	xxx (xx.x)
<b>Respiratory</b>		
Hypoxic respiratory failure	xxx (xx.x)	xxx (xx.x)
<b>Metabolic</b>		
Metabolic	xxx (xx.x)	xxx (xx.x)
<b>Neurological</b>		
Neurological no TBI with brain death	xxx (xx.x)	xxx (xx.x)
Neurological no TBI without brain death	xxx (xx.x)	xxx (xx.x)
<b>Other</b>		
Other	xxx (xx.x)	xxx (xx.x)

Abbreviations: TBI; traumatic brain injury

<b>Table S11: Employment status at day 180</b>			
	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>	<b>P value</b>
<b>Employment status (among participants in paid employment at baseline)– no. (%)</b>			
In paid employment*	xxx (xx.x)	xxx (xx.x)	x.xx
Not in paid employment	xxx (xx.x)	xxx (xx.x)	
<b>Employment status by category for all participants– no. (%)</b>			
<b>Note: Details of subcategories are provided for descriptive purposes only (no statistical comparison between groups will be undertaken due to the large number of categories)</b>			
Working full time	xxx (xx.x)	xxx (xx.x)	
Working part time	xxx (xx.x)	xxx (xx.x)	
On leave but still employed	xxx (xx.x)	xxx (xx.x)	
Temporarily laid off	xxx (xx.x)	xxx (xx.x)	
Unemployed but looking for work	xxx (xx.x)	xxx (xx.x)	
Wanting to work but unemployed due to health	xxx (xx.x)	xxx (xx.x)	
Unemployed and not part of any category	xxx (xx.x)	xxx (xx.x)	
Keeping house or being a home maker	xxx (xx.x)	xxx (xx.x)	
Retired	xxx (xx.x)	xxx (xx.x)	
Receiving disability	xxx (xx.x)	xxx (xx.x)	
Studying	xxx (xx.x)	xxx (xx.x)	
Unknown	xxx (xx.x)	xxx (xx.x)	

\*Patients working full time, part time, or on leave were classified as in paid employment

<b>Table S12: Cognitive function at day 180</b>			
	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>	<b>P value</b>
TICS score	xx.x ± xx	xx.x ± xx	x.xx
<b>Category*</b>			
Severe cognitive impairment	xxx (xx.x)	xxx (xx.x)	

Mild cognitive impairment	xxx (xx.x)	xxx (xx.x)
Ambiguous	xxx (xx.x)	xxx (xx.x)
Non-impaired	xxx (xx.x)	xxx (xx.x)

\*Categories of cognitive function based on the TICS score will be as follows: severe (score ≤20); mild (score 21-25); ambiguous (26-32); and non-impaired (score ≥33)

<b>Table S13: EuroQoL-5D-5L quality of life at 180 days</b>			
	<b>Conservative oxygen therapy group (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>	<b>P value</b>
<b>Mobility – no. (%)</b>			
No problems with walking around	xxx (x.xx)	xxx (x.xx)	x.xx
Slight problems with walking around	xxx (x.xx)	xxx (x.xx)	
Moderate problems with walking around	xxx (x.xx)	xxx (x.xx)	
Severe problems with walking around	xxx (x.xx)	xxx (x.xx)	
Unable to walk around	xxx (x.xx)	xxx (x.xx)	
<b>Personal care – no. (%)</b>			
No problems with washing or dressing	xxx (x.xx)	xxx (x.xx)	x.xx
Slight problems with washing or dressing	xxx (x.xx)	xxx (x.xx)	
Moderate problems with washing or dressing	xxx (x.xx)	xxx (x.xx)	
Severe problems with washing or dressing	xxx (x.xx)	xxx (x.xx)	
Unable to wash or dress	xxx (x.xx)	xxx (x.xx)	
<b>Usual activities (e.g. work, study, housework, family or leisure activities) – no. (%)</b>			
No problems with usual activities	xxx (x.xx)	xxx (x.xx)	x.xx
Slight problems with usual activities	xxx (x.xx)	xxx (x.xx)	
Moderate problems with usual activities	xxx (x.xx)	xxx (x.xx)	
Severe problems with usual activities	xxx (x.xx)	xxx (x.xx)	
Unable to do usual activities	xxx (x.xx)	xxx (x.xx)	
<b>Pain / discomfort – no. (%)</b>			
No pain / discomfort	xxx (x.xx)	xxx (x.xx)	x.xx
Slight pain / discomfort	xxx (x.xx)	xxx (x.xx)	
Moderate pain / discomfort	xxx (x.xx)	xxx (x.xx)	
Severe pain / discomfort	xxx (x.xx)	xxx (x.xx)	
Extreme pain / discomfort	xxx (x.xx)	xxx (x.xx)	
<b>Anxiety / depression – no. (%)</b>			
No anxiety / depression	xxx (x.xx)	xxx (x.xx)	x.xx
Slight anxiety / depression	xxx (x.xx)	xxx (x.xx)	
Moderate anxiety / depression	xxx (x.xx)	xxx (x.xx)	
Severe anxiety / depression	xxx (x.xx)	xxx (x.xx)	
Extreme anxiety / depression	xxx (x.xx)	xxx (x.xx)	
<b>Patient proxy reported health state – mean ± SD</b>	<b>xx ± xx</b>	<b>xx ± xx</b>	<b>x.xx</b>

Abbreviations: SD: standard deviation

<b>Table S14. Subgroup analyses</b>				
	<b>Conservative oxygen therapy (n=xxx)</b>	<b>Standard oxygen therapy (n=xxx)</b>	<b>Difference in medians* (95% CI)</b>	<b>Interaction P value</b>
<b>Median Alive Ventilator-free days (IQR)</b>				
Admission type				x.xx
Surgical	xx(xx-xx)	xx(xx-xx)	x (x-x)	
Non-surgical	xx(xx-xx)	xx(xx-xx)	x (x-x)	
P/F ratio at baseline				x.xx
<300mmHg	xx(xx-xx)	xx(xx-xx)	x (x-x)	
≥300mmHg	xx(xx-xx)	xx(xx-xx)	x (x-x)	
Admission diagnosis				x.xx
Acute brain pathology	xx(xx-xx)	xx(xx-xx)	x (x-x)	
All other diagnoses	xx(xx-xx)	xx(xx-xx)	x (x-x)	
Admission diagnosis				x.xx
Hypoxic ischaemic encephalopathy	xx(xx-xx)	xx(xx-xx)	x (x-x)	
All other diagnoses	xx(xx-xx)	xx(xx-xx)	x (x-x)	

\* Hodges-Lehmann estimate of absolute difference for conservative oxygen minus standard oxygen therapy. The Hodges-Lehmann estimate is the median of all paired differences between observations in the two samples.

**Table S15:** Protocol deviations by treatment group

Description: This table will outline all protocol deviations by treatment group. The format that this table will take in the final manuscript has not been determined.

**FIGURES:**

**Figure 1:** Participant flow diagram

Description: Participant flow diagram with layout as shown in the protocol and statistical analysis plan manuscript.

**Figure 2:** Kaplan-Meier survival estimates of the probably of survival to day 180

Description: Line graph with days 0 to 180 on the horizontal axis and probability of survival on the vertical axis.

## SUPPLEMENTAL FIGURES:

**Figure S1:** Management of patients allocated to the conservative oxygen therapy arm

**Figure S2.** Management of patients allocated to the standard oxygen therapy arm

**Figure S3A:** Mean  $\text{FiO}_2$  by treatment group

Description: Line graph with days 0 to 10 on the horizontal axis and  $\text{FiO}_2$  on the vertical axis with mean daily  $\text{FiO}_2$  shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily  $\text{FiO}_2$  will be calculated from recordings of  $\text{FiO}_2$  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 S3B:** Highest  $\text{FiO}_2$  by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and  $\text{FiO}_2$  on the vertical axis with the highest daily  $\text{FiO}_2$  shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest  $\text{FiO}_2$  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 S3C:** Lowest  $\text{FiO}_2$  by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and  $\text{FiO}_2$  on the vertical axis with the lowest daily  $\text{FiO}_2$  shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest  $\text{FiO}_2$  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 S4A:** Time-weighted mean daily  $\text{PaO}_2$  by treatment group

Description: Line graph with days 0 to 10 on the horizontal axis and  $\text{PaO}_2$  on the vertical axis with mean daily  $\text{PaO}_2$  shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The time-weighted mean daily  $\text{PaO}_2$  will be calculated from recordings of  $\text{PaO}_2$  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 S4B:** Highest daily  $\text{PaO}_2$  by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and  $\text{PaO}_2$  on the vertical axis with the highest daily  $\text{PaO}_2$  shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest  $\text{PaO}_2$  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 S4C:** Lowest  $\text{PaO}_2$  by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and  $\text{PaO}_2$  on the vertical axis with the lowest daily  $\text{PaO}_2$  shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest  $\text{PaO}_2$  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 S5:** Time-weighted-mean daily PaCO<sub>2</sub> by treatment group

Description: Line graph with days 0 to 10 on the horizontal axis and PaCO<sub>2</sub> on the vertical axis with mean daily PaCO<sub>2</sub> shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The time-weighted mean daily PaCO<sub>2</sub> will be calculated from recordings of PaCO<sub>2</sub> 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 S6A:** Mean PEEP by treatment group

Description: Line graph with days 0 to 10 on the horizontal axis and PEEP on the vertical axis with mean daily PEEP shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily PEEP will be calculated from recordings of PEEP 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 S6B:** Highest PEEP by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and PEEP on the vertical axis with the highest daily PEEP shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest PEEP 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 S6C:** Lowest PEEP by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and PEEP on the vertical axis with the lowest daily PEEP shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest PEEP 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 S7A:** Mean airway pressure by treatment group

Description: Line graph with days 0 to 10 on the horizontal axis and mean airway pressure on the vertical axis with mean daily mean airway pressure shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily mean airway pressure will be calculated from recordings of mean airway pressure 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 S7B:** Highest mean airway pressure by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and mean airway pressure on the vertical axis with the highest daily mean airway pressure shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest mean airway pressure 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 S7C:** Lowest mean airway pressure by treatment group

Description: Line graph with days 0 to 28 on the horizontal axis and mean airway pressure on the vertical axis with the lowest daily mean airway pressure shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest mean airway pressure 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 S8:** Predominant modes of ventilation by treatment group

Description: Stacked bar chart with days 0 to day 28 on the horizontal axis and percentage of participants on the vertical axis. The number of participants remaining in ICU on each day will be indicated on the horizontal axis. The percentage of participants remaining in ICU receiving each of the top five most commonly used modes on each day based on categories shown in Table S2 will be displayed on a stacked bar chart by treatment group. On each day participants not receiving one of the top five categories of treatment for that day will be categorised as either: (i) invasively ventilated (other); (ii) not invasively ventilated but receiving supplemental oxygen; or (iii) not ventilated and not receiving supplemental oxygen. Any missing data will be described in a footnote to the figure.

**Figure S9:** GOSE categories at 180 days for patients with acute brain pathologies at baseline

Description: Stacked horizontal bar chart with GOSE categories at day 180 for patients with acute brain pathologies at baseline by treatment group.