The REST Trial

pRotective vEntilation with veno-venouS lung assisT in respiratory failure

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STATISTICAL ANALYSIS PLAN

Version 1.0 *[Final]* *16/12/19*

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This document and all preceding versions will be stored in the Trial Master File for this trial

Contents

ABBREVIATIONS

ABBREVIATION	DEFINITION
ABG	Arterial Blood Gas
AD8	AD8 Dementia Screening Interview
ADE	Adverse Device Effect
AE	Adverse Event
APACHE ll	Acute Physiology and Chronic Health Evaluation score
APRV	Airway Pressure Release Ventilation
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
CL	Clinical Lead
CMP	Case Mix Programme
CO_2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DNAR	Do Not Attempt Resuscitation
$ECCO_2R$	Extracorporeal Carbon Dioxide Removal
ECMO	Extracorporeal Membrane Oxygenation
EQ-5D-5L	EuroQoL-5 Dimension Questionnaire (5 level version)
FiO_2	Fraction of Inspired Oxygen
GP	General Practitioner
HDU	High Dependency Unit
HFOV	High Frequency Oscillatory Ventilation
HRQoL	Health Related Quality of Life
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
ICNARC	Intensive Care National Audit & Research Centre
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
MoCA-BLIND	Montreal Cognitive Assessment/MoCA-Blind
NHS	National Health Service
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
NMBD	Neuromuscular Blocking Drugs
$PaCO_2$	Partial Pressure of Carbon Dioxide in arterial blood
PaO_2	Partial Pressure of Oxygen in arterial blood
PBW	Predicted Body Weight
PEEP	Positive End Expiratory Pressure

P/F Ratio	PaO_2/FiO_2 ratio
PTSS 14	Post Traumatic Stress Syndrome Questionnaire
QoL	Quality of Life
RR	Respiratory Rate
SADE	Severe Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGRQ	St George's Respiratory Questionnaire
SICSAG	Scottish Intensive Care Society Audit Group
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedures
TAPSE	Tricuspid Annular Plane Systolic Excursion
TSC	Trial Steering Committee
USADE	Unanticipated Suspected Serious Adverse Device Effect
VFDs	Ventilator Free Days
Vt	Tidal Volume
VV-$ECCO_2R$	Veno-venous Extracorporeal Carbon Dioxide Removal

1. BACKGROUND AND DESIGN

The aim of this study proposes to deliver a multi-centre clinical trial to determine whether veno-venous extracorporeal carbon dioxide removal (VV-ECCO$_2$R) and lower tidal volume mechanical ventilation improves outcomes and is cost-effective, in comparison with standard care in patients who are mechanically ventilated for acute hypoxaemic respiratory failure. Hypothesizing that in adult patients who require invasive mechanical ventilation for acute hypoxaemic respiratory failure, VV-ECCO$_2$R and lower tidal volume ventilation results in reduced mortality.

This is a randomised, allocation concealed, controlled, open, pragmatic clinical and cost effectiveness trial. The study objectives are as follows:

1.1 Primary objective

To determine whether VV-ECCO$_2$R and lower tidal volume mechanical ventilation in patients with acute hypoxaemic respiratory failure decreases mortality 90 days after randomisation.

1.2 Secondary objectives

In mechanically ventilated patients with acute hypoxaemic respiratory failure we want to determine the effects of VV-ECCO$_2$R on:

i. Tidal volumes
ii. Duration of mechanical ventilation
iii. Requirement for Extracorporeal Membrane Oxygenation (ECMO)
iv. Long-term mortality
v. Health Related Quality of Life
vi. Safety
vii. Cost-effectiveness in the NHS setting
viii. Long term respiratory morbidity

Patients will need to be assessed using the inclusion and exclusion criteria as set out below. Eligibility to participate in the trial will be confirmed by a medically qualified person who is

named on the Delegation Log. The medical care given to, and medical decisions made on behalf of subjects will be the responsibility of an appropriately qualified treating physician.

Two arterial blood gas samples (ABG) will be required but these will be collected as part of standard care. The P/F ratio table in appendix 1 can be used for reference.

Patients will be eligible to participate in the study if they fulfil the following criteria:

1.3 Inclusion criteria

- Invasive mechanical ventilation using PEEP ≥ 5cmH_2O*
- Acute and potentially reversible cause of acute respiratory failure as determined by the treating physician
- Within 48 hours of the onset of hypoxaemia as defined by $PaO_2/FiO_2 \leq 20kPa$**

*Recommended on low tidal volume ventilation ≤ 6ml/kg PBW

**Requires two ABG with a PaO2/FiO2 ≤ 20kPa separated by at least 6 hours. 48 hour duration to consent begins at the time of 2nd ABG demonstrating PaO2/FiO2 ratio ≤ 20kPa. Site will then have a further 8 – 24 hours to randomise and administer the intervention. The onset of hypoxaemia is from time of intubation and invasive ventilation.(ABGs with $PaO_2/FiO_2 \geq 20kPa$ are permitted between the two trial inclusion ABGs).

1.4 Exclusion criteria

- Age < 16 years old
- Intubated and mechanically ventilated via an endotracheal or tracheostomy tube ≥ 7 days (168 hours) up to the time of randomisation
- Ability to maintain Vt to ≤ 3ml/kg PBW while maintaining pH ≥ 7.2 as determined by the treating physician*
- Receiving, or decision to commence, ECMO in the next 24 hours.
- Mechanical ventilation using High Frequency Oscillatory Ventilation (HFOV) or Airway Pressure Release Ventilation (APRV)
- Untreated pulmonary embolism, pleural effusion or pneumothorax as the primary cause of acute respiratory failure.

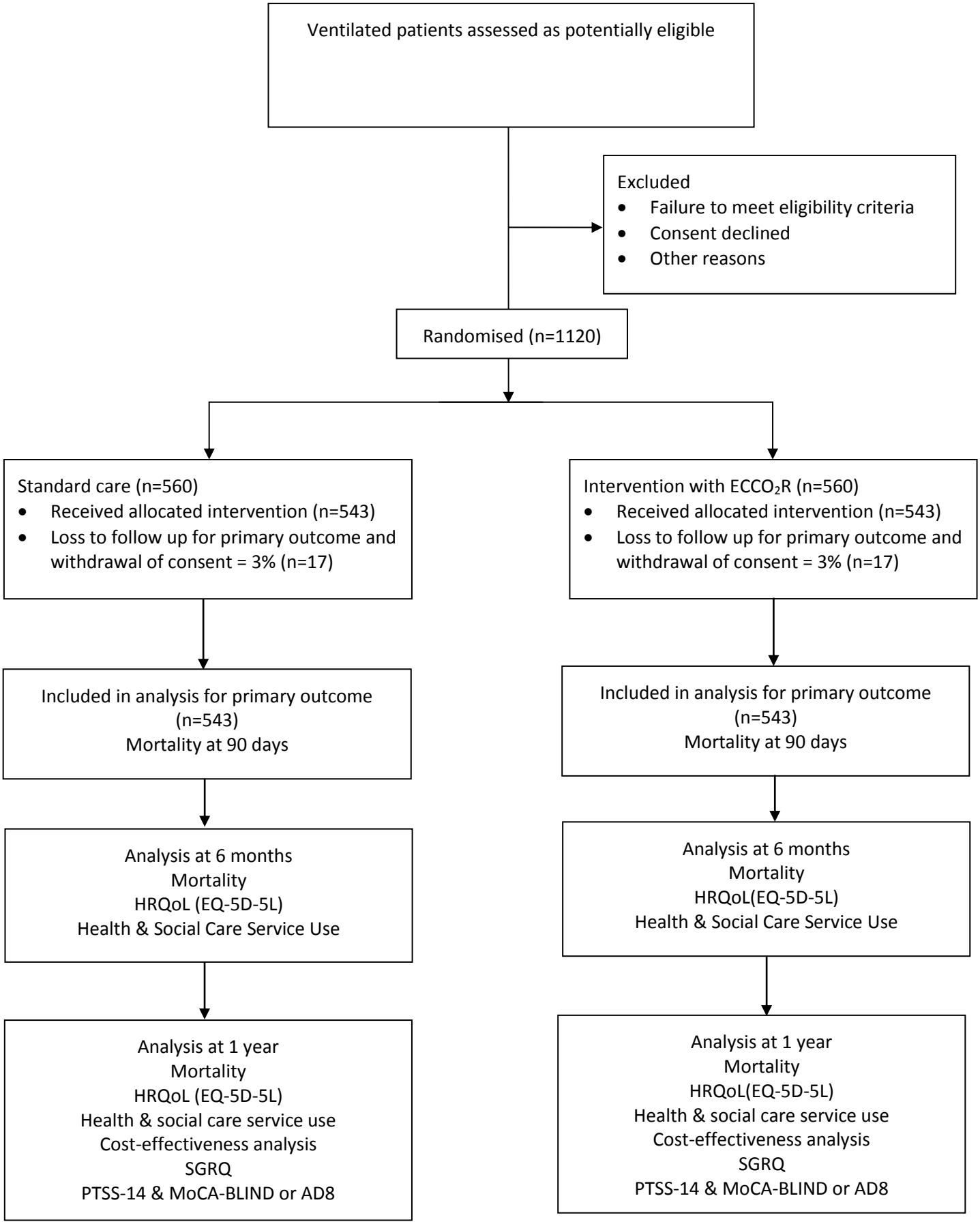
- Acute respiratory failure fully explained by left ventricular failure or fluid overload (May be determined by clinical assessment or echocardiography/cardiac output monitoring).
- Left ventricular failure requiring mechanical support
- Contra-indication to limited systemic anticoagulation with heparin
- Unable to obtain vascular access to a central vein (internal jugular or femoral vein)
- Inferior vena cava filter (if using femoral vein catheter)
- Consent declined
- Treatment withdrawal imminent within 24 hours
- Patients not expected to survive 90 days on basis of premorbid health status
- Do Not Attempt Resuscitation (DNAR) order (excluding advance directives) in place
- Severe chronic respiratory disease requiring domiciliary ventilation (except for sleep disordered breathing)
- Severe chronic liver disease (Child Pugh >11)
- Platelet count < 40,000 mm^3 (Prior to catheter insertion)
- Previously enrolled in the REST trial
- Prisoners

* This exclusion criterion relates to whether a Vt ≤ 3ml/kg PBW could be achieved without the need for $ECCO_2R$. A tidal volume ≤ 3ml/kg is unlikely to be achievable in most clinical scenarios without $ECCO_2R$ as it is approaching dead space ventilation.

Full details of the background to the trial and its design are presented in the protocol.

1.5 Study Schematic Diagram

Figure 1: Study Schematic



2. OUTCOME MEASURES

2.1 Primary outcome measure(s)

All cause mortality 90 days after randomisation

2.2 Secondary outcome measures

I. Tidal volume (ml/kg PBW) at day 2 and day 3 after randomisation
II. Ventilator free days at 28 days after randomisation
III. Duration of ventilation in survivors after randomisation at 28 days
IV. Need for ECMO up to Day 7
V. Mortality rate at 28 days, 6 months and 1 year after randomisation
VI. Health Related Quality of Life (HRQoL) at 6 months and 1 year after randomisation
VII. Adverse event rate
VIII. Health & Social Care Service costs at 6 months and 1 year
IX. St George's Respiratory Questionnaire (SGRQ) at 1 year and need for home oxygen at 6 months and 1 year after randomisation
X. Post Traumatic Stress Syndrome Questionnaire (PTSS-14) at 1 year after randomisation
XI. Montreal Cognitive Assessment (MoCA-BLIND) or AD8 Dementia Screening Interview (AD8) at 1 year after randomisation

2.3 Exploratory Outcome Measures

Right heart function as determined by echocardiography during 6ml/kg PBW and ≤3ml/kg PBW tidal volume ventilation (ECHO data will only be collected at a selected number of sites).

3. DATA

3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are described in the trial protocol.

A copy of the CRFs and questionnaires (e.g. Quality of Life (QoL) questionnaires) are presented in the Trial Master File.

3.2 Management of datasets

At the time of analysis:

The Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the SOP DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

3.3 Data completion schedule

Study Visits and Procedures

Clinical data will be collected during trial participants stay in the ICU up to 28 days after randomisation. For routinely collected clinical data the NHS record will be the source document and for study specific clinical measurements the CRF will be the source document.

Day 0 (baseline)

Day 0 is 24 hours prior to randomisation. If more than one value is available for this 24-hour period, the value closest but prior to the time of randomisation will be recorded. Day 0 (baseline) data collected will include but is not limited to:

- Patient demographics (date of birth, gender, measured height)
- ICNARC Case Mix Programme (CMP) number
- Scottish Intensive Care Society Audit Group (SICSAG) number
- Date/time of consent and randomisation
- Date and time of ICU admission
- Admission diagnostic category
- Assessment of functional status
- Presence of Acute Respiratory Distress Syndrome (ARDS) and aetiology
- Date/time of onset of mechanical ventilation
- The Acute Physiology and Chronic Health Evaluation score (APACHE II)

- PaO_2/FiO_2 ratio (Qualifying PaO_2 /FiO_2 ratios including date/time)
- Date and time of worst PaO_2/FiO_2 ratio
- Determinants of Sequential Organ Failure Assessment (SOFA) score
- Ventilation parameters including but not limited to: Mode of ventilation, minute volume, RR, mean airway pressure, plateau pressure, PEEP
- Arterial blood gas including but not limited to FiO_2, PaO_2, $PaCO_2$,pH
- Date/time onset of $ECCO_2R$ therapy (from commencement of CO_2 removal)
- Use of adjunctive therapies including Neuromuscular Blocking Drugs (NMBD) and prone position
- Echocardiography parameters including but not limited to ventricular size and function and tricuspid annular plane systolic excursion (TAPSE)

Daily Data:

Day 1 is from the time of randomisation to the end of that calendar day. If more than one value is available for this period, the value closest but after the time of randomisation will be recorded. All other daily measurements will be recorded and collected between 6-10am or as close to this time as possible, unless otherwise stated in the CRF. Daily data will be collected to day 7 and will include but is not limited to:

- Ventilation parameters including but not limited to: Mode of ventilation, minute volume, RR, mean airway pressure, plateau pressure, PEEP
- Arterial blood gas including but not limited to FiO_2, PaO_2, $PaCO_2$, pH
- CO_2 removal rate while on $ECCO_2R$ therapy
- Commencement or transfer for ECMO following randomisation
- Use of adjunctive therapies including NMBD and prone positioning
- Blood product administration (blood, platelets, fresh frozen plasma, cryoprecipitate or other)
- Adverse events

Day 1 and 2:
Echocardiography parameters including but not limited to ventricular size and function and TAPSE.

Day 3 and 7

- Determinants of SOFA score

28 days:

- Adverse Events

6 months:

- EuroQoL-5 Dimension Questionnaire (EQ-5D-5L) (Post or telephone)
- Patients use of health and social care resources collected by resource logs

1 year:

- EQ-5D-5L (Post or telephone)
- Patients use of health and social care resources collected by resource logs
- SGRQ
- PTSS-14
- MoCA-Blind or AD8

The following data will also be collected

- Date of discontinuation of $ECCO_2R$ and reason
- Date of discontinuation of mechanical ventilation (unassisted breathing)
- Date of critical care discharge
- Date of hospital discharge
- Date of death

Follow Up Visits and Procedures

HRQoL and Health and Social Care Service use will be assessed at 6 months and 1 year after randomisation. Patients will also be required to complete the SGRQ at 1 year.

The CTU will also collect mortality data at 1, 2 and 5 years post randomisation.

3.4 Data verification

Study specific data validation checks will be implemented. The process of data validation ensuring the accuracy and quality of the data will be carried out according to SOP DM04 Data Validation and Discrepancy Management.

3.5 Data coding

The variable codings will be as specified on the CRF.

4. DEFINITION OF TERMS

Term	Definition
Discharge from critical care	First discharge to a medical ward in the hospital or another hospital; a transfer between ICUs is not considered a discharge from critical care.
Hospital discharge	Hospital discharge is the first date that the patient is discharged to home/ community, a transfer between hospitals is not considered as a hospital discharge
Unassisted breathing i.e. no ventilatory support	Extubated with supplemental oxygen, or room air, or open T-tube breathing, or tracheostomy mask breathing, or CPAP ≤ 5 cm H_2O without pressure support for a calendar day. Patients receiving pressure support via non-invasive ventilation will be defined as receiving ventilatory support (except for sleep disordered breathing).
VFDs to day 28	The number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing

	to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.
Duration of ventilation	Counted from recruitment to the end of the last period of assisted breathing

5. SAMPLE SIZE CALCULATIONS

The required sample size is 1120 patients. With 90% power at a p value of 0.05 with a 3% dropout, 560 per group will be required to detect a 23% relative reduction (9% absolute reduction) in 90 day mortality, assuming a control group mortality of 41%. This sample size would also detect a 20% relative reduction (8% absolute reduction) at 80% power.

We have used two independent sources for the estimation of the all-cause mortality that was used to determine the sample size:

1. Data from the Intensive Care National Audit and Research Centre (ICNARC) case mix programme (CMP) for UK intensive care patients. The unpublished ICNARC data from the CMP for the year 2012 was compiled from 133,266 admissions from 203 adult critical care units in England, Wales and Northern Ireland. For patients with a PaO_2/FiO_2 ratio < 20kPa the ICU mortality was 40.7% and the hospital mortality was 48.8%.
2. Data from the NIHR HTA funded OSCAR trial (30). This was a recent large randomised controlled trial on high frequency oscillatory ventilation (HFOV) in patients with respiratory failure. The 30-day mortality in the control group in the OSCAR trial was 41.1%. These patients received conventional ventilation with a tidal volume of 6-8ml/kg PBW and had an average PaO_2/FiO_2 ratio of 15kPa.

We have assumed 90-day control group mortality will be at least equivalent to 41%. We have used the effect size of one of the few interventions to reduce mortality in patients with hypoxaemic respiratory failure. The ARDSNet ARMA trial demonstrated a 9% absolute risk reduction in patients with hypoxaemic respiratory failure secondary to ARDS with lung protective ventilation. Our hypothesis is that we can extend the benefits of more protective lung ventilation with the use of $ECCO_2R$. Loss to follow up in UK critical care trials is low. We know this is approximately 3% from previously published research as well as from the experience of our team in managing large critical care trials in the UK.

An independent statistician (for the DMEC) will conduct an interim analysis for the primary outcome measure (mortality) before the recruitment of 560 patients; (half the estimated sample size), to ascertain whether the assumptions made in the sample size calculations are correct.

6. RANDOMISATION AND BLINDING

6.1 Randomisation

Once consent has been obtained for the patient to participate in the study the patient will be randomised to either $ECCO_2R$ with lower tidal volume mechanical ventilation or standard care. Patients will be randomised via a central randomisation system and sites will be provided with trial specific randomisation guidelines. Randomisation will be completed by an appropriately trained and delegated member of the research team.

Randomisation will be stratified by recruitment centre.

Participants will be allocated to $ECCO_2R$ with lower tidal volume mechanical ventilation or standard care on a 1:1 ratio. At the time of randomisation, each patient will be allocated a unique Participant Study Number, which will be used throughout the study for participant identification. An entry will be recorded in the patient medical notes noting enrolment into the study.

The research team will then ensure that the clinical team are informed which treatment this process has allocated. They will liaise with the clinical team as required to ensure that the allocated treatment is administered. If allocated VV-ECCO$_2$R, this should ideally be commenced within 8 hours of randomisation.

6.2 Blinding and Allocation Concealment

Only the allocation of the intervention will be concealed; once assigned to the standard care or intervention group the interventions will be unblinded to the trial participant's representative (and to the participant on regaining capacity), research team, care providers, data analysts and outcome assessors. By the nature of the intervention it will not be possible to blind clinicians to whether a participant has been randomised to ECCO$_2$R or standard care.

7. ANALYSIS PRINCIPLES

The primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis.

Standard approaches will be used to detect patterns in missing data. Baseline characteristics, follow-up measurements and safety data will be described using the appropriate descriptive summary measures depending on the scale of measurement.

For the primary outcome and other dichotomous outcomes, risk ratios and 95% confidence interval (CI) will be calculated. The primary outcome of 90 day mortality will be analysed using chi-square and a secondary analysis using logistic regression to adjust for age, SOFA score, Baseline PaO_2 /FiO_2 and Baseline Plateau Pressure will also be carried out. The comparison of continuous outcomes between the two groups will be investigated using analysis of variance/analysis of covariance (if baseline measurements available), adjusting for other covariates where appropriate. Time-to-event outcomes will be analysed by survival methods and reported as hazard ratios with 95% CI. The intention-to-treat basis analysis will use a significance level of <0.05 for the primary outcome. Sensitivity analysis will be performed for the primary outcome excluding the first two intervention arm patients at each site in order to address potential learning effects. This would be explored further using a power curve model.

Per protocol analysis will also be carried out for the secondary outcome of Tidal Volume at Days 2 and 3 i.e. including those who were on VV-ECCO$_2$R on day 2 and 3 in the intervention arm. Estimates of effects/association and 95% CI will be reported for secondary and exploratory outcomes.

An independent statistician (for the DMEC) will conduct an interim analysis for the primary outcome measure before the recruitment of 560 patients. Using the chi-square statistic (mortality by treatment group), a p value less than 0.001 will be used according to the Haybittle-Peto stopping rule.

7.1 Subgroup analyses

Exploratory analyses will be reported using 99% confidence intervals. Logistic regression will be used with interaction terms (treatment group by subgroup) for the following subgroups:

(i) Presence of ARDS prior to randomisation
(ii) Baseline PaO_2 /FiO_2 ratio prior to randomisation (<50/50-99/100-150)
(iii) Baseline Plateau Pressure prior to randomisation quartiles
(iv) Volume of ECCO$_2$R participants at center (<10/>=10)
(v) Vasopressor requirement prior to randomisation (yes/no)
(vi) Baseline $PaCO_2$ prior to randomisation quartiles
(vii) Baseline driving pressure prior to randomisation quartiles
(viii) Baseline risk of death score (Apache II) quintiles prior to randomisation.

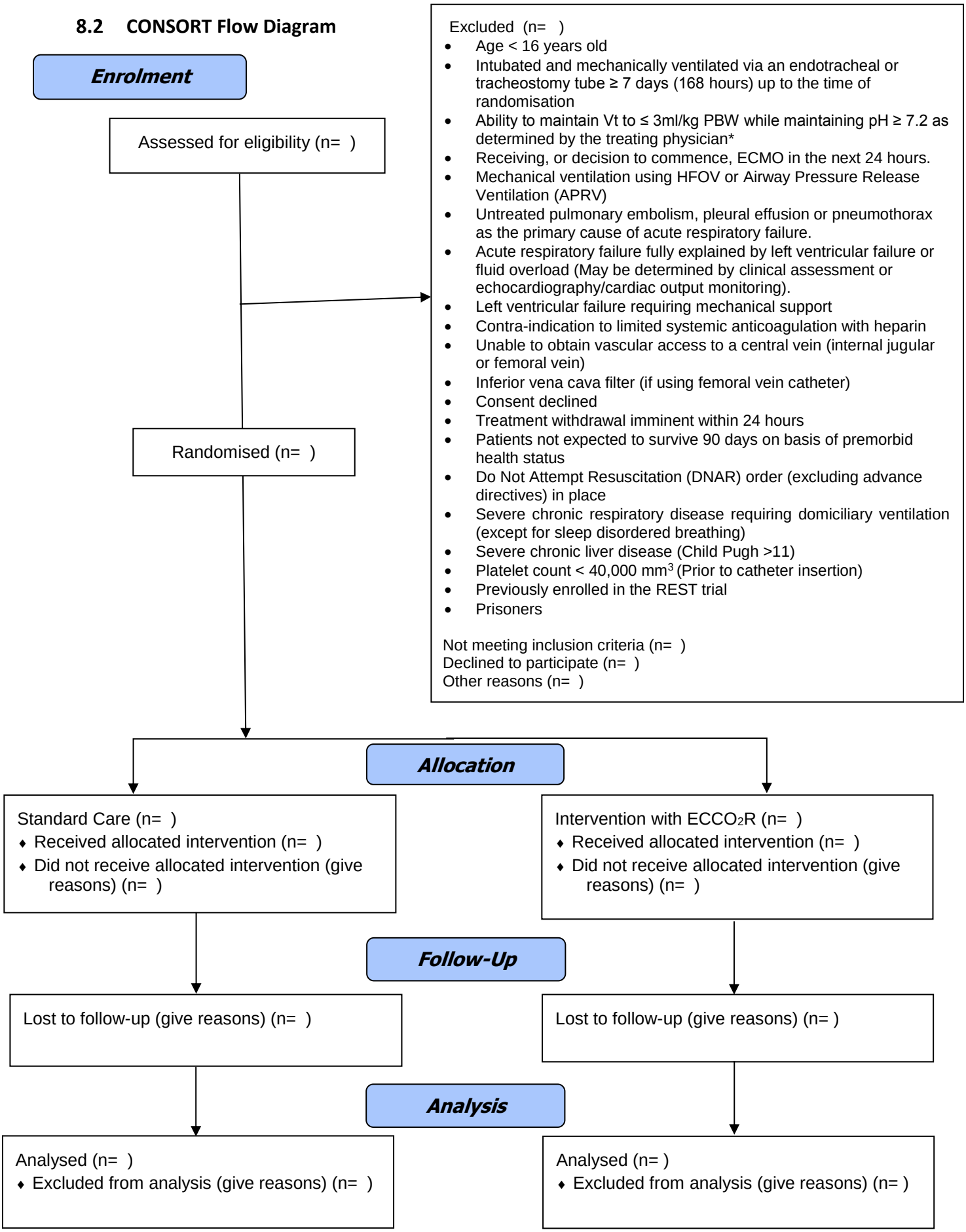
8. ANALYSIS DETAILS

The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

8.1 Recruitment and follow-up patterns

- Recruitment by site
- Withdrawals by site
- Mortality 1, 2 and 5 years post randomisation

8.2 CONSORT Flow Diagram



8.3 Baseline Characteristics

- Age, mean (SD) by treatment arm
- Gender, no. (%) by treatment arm
- Dependency prior to hospital admission, no. (%) by treatment arm
- Height (cm), mean (SD) by treatment arm
- Predicted body weight (kg), mean (SD) by treatment arm
- Admission diagnostic category, no. (%) by treatment arm
- Presence of ARDS, no. (%)by treatment arm
- Aetiology of Ards, no. (%) by treatment arm
- APACHE II score, mean (SD) by treatment arm
- Arterial blood gas $PaCO_2$, mean (SD) by treatment arm
- PaO_2/FiO_2 ratio closest to but prior to randomisation, mean (SD) by treatment arm
- Second qualifying PaO_2/FiO_2 ratio, mean (SD) by treatment arm
- Worst PaO_2/FiO_2 ratio, mean (SD) by treatment arm
- Arterial pH, mean (SD) by treatment arm
- Total SOFA score, mean (SD) by treatment arm
- Mode of ventilation, no. (%) by treatment arm
- Use of Adjunctive therapies, no. (%) by treatment arm
- Mean airway pressure (cmH_2O), mean (SD) by treatment arm
- PEEP (cmH_2O), mean (SD) by treatment arm
- Plateau Pressure (cmH_2O), mean (SD) by treatment arm
- Total Respiratory Rate (breaths/min), mean (SD) by treatment arm
- Minute Volume (L/min), mean (SD) by treatment arm
- Tidal Volume (ml/kg PBW), mean (SD) by treatment arm

8.4 Trial treatment

- Treatment allocation (Intervention), no. (%) commencing $ECCO_2R$
- Adherence to protocol-specified intervention, no. (%) by treatment arm receiving $ECCO_2R$ for >48 hrs
- Duration of $ECCO_2R$ mean(SD) days

8.5 Trial Outcomes

- All-cause mortality 90 days after randomisation, no (%) by treatment arm, Risk ratio 95% CI
- Tidal Volume (ml/kg PBW) at days 2 and 3 after randomisation, mean (SD) by treatment arm, difference in mean with 95% CI
- Ventilator free days at 28 days after randomisation, mean (SD) by treatment arm, difference in mean with 95% CI
- Ventilation duration in survivors after randomisation at 28 days, mean (SD) by treatment arm, difference in mean with 95% CI
- Need for ECMO up to day 7, no (%) by treatment arm, Risk ratio 95% CI
- Mortality rate at 28 days after randomisation, no (%) by treatment arm, Risk ratio 95% CI
- Mortality rate at 6 months after randomisation, no (%) by treatment arm, Risk ratio 95% CI
- Mortality rate at 1 year after randomisation, no (%) by treatment arm, Risk ratio 95% CI
- SGRQ at 1 year after randomisation, Symptoms score, Activity score, Impacts score and Total score mean (SD) by treatment arm, difference in mean with 95% CI
- Need for home oxygen at 6 months and 1 year after randomisation, no (%) by treatment arm, Risk ratio 95% CI
- Post Traumatic Stress Syndrome Questionnaire (PTSS-14) at 1 year after randomisation, mean (SD) by treatment arm, difference in mean with 95% CI
- Montreal Cognitive Assessment (MoCA-BLIND) or AD8 Dementia Screening Interview (AD8) at 1 year after randomisation, mean (SD) by treatment arm, difference in mean with 95% CI
- Right heart function as determined by echocardiography during 6ml/kg PBW and ≤3ml/kg PBW tidal volume ventilation. Echocardiography parameters including but not limited to ventricular size and function and TAPSE, mean (SD) by treatment arm, difference in mean with 95% CI

8.6 Toxicity/ Symptoms

- Adverse Event Rate, no. events (%) by treatment arm , no. patients (%) by treatment arm. Risk Ratio and 95% CI.

  AEs of interest are as follows:

  Device failure causing AE
  Haemolysis
  Bleeding
  - At cannula site
  - Other site

  Infectious complications
  Heparin induced thrombocytopenia

- Adverse Device Effect, no. events (%) by treatment arm, no. patients (%) by treatment arm. Risk Ratio and 95% CI.
- Serious Adverse Event, no. events (%) by treatment arm and System Organ Class, no. patients (%) by treatment arm. Risk Ratio and 95% CI.
- Serious Adverse Device Effect, no. events (%) by treatment arm and System Organ Class, no. patients (%) by treatment arm. Risk Ratio and 95% CI.
- Unanticipated Serious Adverse Device effect, no. events (%) by treatment arm and System Organ Class, no. patients (%) by treatment arm. Risk Ratio and 95% CI.

8.7 Health Economics

Details of the Health Economics analysis will be outlined in a separate Health Economics Analysis Plan.

9. ADDITIONAL INFORMATION

9.1 Trial Steering Committee (TSC)

The TSC will provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. An independent chair will lead the TSC, with at least 75% independent membership. Membership and roles of the TSC will be listed in the TSC Charter. The TSC will incorporate a patient/public representative as well as the CI and CL.

The TSC will meet at least annually and observers may be invited and be in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the CTU.

9.2 Data Monitoring and Ethics Committee (DMEC)

The independent DMEC will be comprised of at least 2 independent clinicians with experience in clinical trials, and an independent statistician. One of the independent clinicians will have experience in the regulatory aspects of clinical trials involving medical devices.

The role of the independent DMEC will be detailed in the DMEC charter but will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies. The independent DMEC will meet at least 6 monthly and additional meetings can be convened if the event of any safety concerns.

If funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

10. SIGNATURES OF APPROVAL

Date: 24th December 2019

Version: 1.0 Final

This document has completed a final review and is understood and approved by the following:

Danny McAuley	*Chief Investigator Signature*	24.12.2019 Date dd/mm/yyyy
Clíona McDowell	*Head of Statistics*	24/12/2019 Date dd/mm/yyyy
Clíona McDowell	*Study Statistician Signature*	24/12/2019 Date dd/mm/yyyy

Appendix 1: P/F ratio reference table for inclusion criteria

FiO_2	**Maximum PaO_2 if P/F ratio ≤ 20kPa**
0.50	10.0 kPa
0.55	11.0 kPa
0.60	12.0 kPa
0.65	13.0 kPa
0.70	14.0 kPa
0.75	15.0 kPa
0.80	16.0 kPa
0.85	17.0 kPa
0.90	18.0 kPa
0.95	19.0 kPa
1.00	20.0 kPa

Appendix 2: PEEP/FiO2 table

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

APPENDIX 3: EXAMPLE DRAFT SUMMARY TABLES

Figure xxx. Recruitment by Site

Figure xxx. Withdrawals by Site

Table x.x.x. Baseline Characteristics at trial entry

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**
Age (years)		
Gender Male Female		
Dependency prior to hospital admission Able to live without assistance in daily activities Minor assistance with some daily activities Major assistance with majority of/all daily activities Total assistance with all daily activities		
Height (cm) Measured length of patient (heel to crown)		
Predicted body weight (kg)		
Admission diagnostic category Central Nervous System Central Vascular System Respiratory System GIT Hepatology Renal Toxicology Haematology Orthopaedic Sepsis Other		
Presence of ARDS		
Aetiology of ARDS		

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**
Smoke/toxin inhalation Gastric content aspiration Near drowning Thoracic trauma Pneumonia Sepsis Cardiopulmonary bypass Pancreatitis Non-thoracic trauma Other		
APACHE II score		
Arterial blood gas $PaCO_2$		
PaO_2:FiO_2 ratio		
Worst PaO_2/FiO_2 ratio		
Second qualifying PaO_2/FiO_2 ratio		
Arterial pH		
Total SOFA Score		
Mode of Ventilation Mandatory, no spontaneous additional breaths above the fixed respiratory rate Spontaneous, no back up mandatory breaths Mixed, Mandatory and spontaneous breaths Other		
Use of Adjunctive therapies NMBD PP INO Other		
Mean airway pressure (cmH_2O)		
PEEP (cmH_2O)		
Plateau Pressure (cmH_2O)		

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**
Total Respiratory Rate (Breaths/min)		
Minute volume (mL/min)		
Tidal Volume (mls/kg PBW)		

Mean (SD) presented for continuous variables and no. (%) for all categorical variables.

Table x.x.x. Treatment after Trial Entry

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**
Treatment Allocation Adherence to protocol-specified intervention No. of days on $ECCO_2R$*		
Reasons for $ECCO_2R$ Discontinuation • The patient's legal representative has requested witdrawal from the study • There has been a safety concern about the therapy such that withdrawal is mandated • $ECCO_2R$ therapy has been weaned • 7 days post randomisation • Escalation to ECMO has occurred • Discontinuation of active medical treatment has occurred • The patient has died • Other		
Protocol Deviations: Eligibility Treatment Process Other		

*Mean (SD) no. of days on $ECCO_2R$

Table x.x.x Main Clinical Outcome variables

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**	**Difference (95% CI)**	**p-value**
Primary outcome; Mortality 90 days post randomisation[#]				
VFDs 28 days post randomisation				
Ventilation duration post randomisation All Survivors Non-survivors				
Need for ECMO to day 7 Yes No[#]				
Mortality rate at 28 days post randomisation[#]				
Mortality rate at 6 months post randomisation[#]				
Mortality rate at 1 year post randomisation[#]				
SGRQ • Symptoms Score • Activity Score • Impacts Score • Total Score				
Need for home oxygen at 1 year post randomisation[#]				
PTSS-14 Score				
MoCA-Blind				
AD8 Dementia Screening				

Mean (SD) presented for treatment arms
[#]No. (%) for treatment arms and Risk Ratio and 95% CI presented

Figure x.x.x. Kaplan Meier Curve

Time to death and no. of deaths on x-axis

Table x.x.x. Tidal Volume after Randomisation

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**	**Mean Difference (95% CI)**
Tidal volume ml/kg PBW Day 2 Day 3 Day 4 Day 5 Day 6 Day 7			
Tidal volume ml/kg PBW* Day 2 Day 3			

Mean (SD) and Min/Max presented for TV and no. (total % out of 40) for recruitment rate.

*Per protocol population i.e. those who were on VV-$ECCO_2R$ on day 2 and 3 in the intervention arm

Table x.x.x. Safety by Treatment Group

		Number of events			Number of patients			
		Total n	**Intervention $ECCO_2R$ n (%)**	**Standard Care n (%)**	**Total n (%)**	**Intervention $ECCO_2R$ n (%)**	**Standard Care n (%)**	**RR(95%CI)**
AEs, SAEs, ADE, SADE, USADE	Total SAEs							
	Related to study device							
	Related to study device and unanticipated							
	Total AEs							
	Related to study device							
SAEs	Cardiac Disorders							
	Hepatobiliary disorders							
	Respiratory, thoracic and mediastinal disorders							
	etc…..							
AEs	Device failure causing AE							
	Haemolysis							
	Bleeding at cannula site							
	Bleeding at other site							
	Infectious complications							
	Heparin induced thrombocytopenia							
Adverse Device effect								
Serious Adverse Device effect								

Unanticipated Serious Adverse Device effect								

For no. of events %s are calculated within total SAEs, AEs, ADEs and SADEs respectively within treatment arm.

Table xxx. Follow-up Questionnaires at 1 year

	$ECCO_2R$ Intervention n = (%)	**Standard Care n = (%)**	**Difference (95% CI)**
Saint Georges Questionnaire			
PTSS-14			
MoCA			
AD8			

Figure x.x.x. Subgroup Analyses

OR and 99% CI will be presented graphically alongside the n(%) for interaction terms for the following pre-specified subgroups

	Treatment Group		
	Intervention $ECCO_2R$	**Standard Care**	**Difference (99% CI)**
Presence of ARDS prior to randomisation Yes No			
Baseline PaO_2 /FiO_2 ratio prior to randomisation <50 50-99 100-150			
Baseline Plateau Pressure prior to randomisation Quartile 1 Quartile 2 Quartile 3 Quartile 4			
Volume of $ECCO_2R$ participants at center <10 cases >=10 cases			

	Treatment Group		
	Intervention $ECCO_2R$	**Standard Care**	**Difference (99% CI)**
Vasopressor requirement prior to randomisation Yes No			
Baseline $PaCO_2$ prior to randomisation Quartile 1 Quartile 2 Quartile 3 Quartile 4			
Duration of Carbon Dioxide (CO_2) removal Quartile 1 Quartile 2 Quartile 3 Quartile 4			
Baseline driving pressure prior to randomisation Quartile 1 Quartile 2 Quartile 3 Quartile 4			
Baseline risk of death score (Apache II) quintiles prior to randomisation Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5			

Table x.x.x. Exploratory Outcome Measures

	Treatment Group		
	Intervention $ECCO_2R$	**Standard Care**	**Difference (99% CI)**
Baseline / Day 0: • Tricuspid annular plane systolic excursion (TAPSE) measured in cm • Right ventricular strain (RVS) measured in percentage • Right ventricle fractional area of change (FAC) measured in percentage • Right ventricle end diastolic area to Left ventricle end diastolic ratio (EDA ratio) measure as a ratio (e.g. 0.6) • Left ventricular end diastolic diameter measured in cm • Left ventricle function measured in percentage			
Day 1 or 2: • TAPSE measured in cm • RVS measured in percentage • Right Ventricle FAC measured in percentage • Right ventricle EDA ratio • Left ventricle end diastolic diameter measured in cm • Left ventricle function measured in percentage			