IMPERIAL

CLINICAL STUDY PROTOCOL

Full Study Title: **Rest Or Moderate mechanical ventilation during ECMO support**

Acronym: **ROMEO**

Sponsor: **Imperial College London**

Version no: **1.0**

Protocol Date: **19th SEPTEMBER-2025**

This protocol has regard for the HRA guidance

This project (NIHR158537) apart from the Tertiary Mechanistic Outcomes and Mechanistic Analyses, is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership.

The views expressed are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

RESEARCH REFERENCE NUMBERS

IRAS ID:	**351190; (IRAS Scotland 359602)**
REC Reference Numbers:	**25/LO/0660; (25/SS/0077 Scotland)**
ISRCTN Number:	**70543115**
Sponsor Protocol Number:	**175660**
Funder reference:	**NIHR158537**

Keywords:

Ventilator Induced Lung Injury / Acute Respiratory Distress Syndrome / Extracorporeal Membrane Oxygenation / Mechanical Ventilation / Mechanical Power / Near Apnoeic Ventilation (NAV)

CONTACT LIST

Chief Investigator

Dr Brijesh V Patel
Anaesthetics, Pain Medicine, & Intensive Care
Department of Surgery and Cancer, Faculty of Medicine,
Imperial College London.

Adult Intensive Care Unit,
Royal Brompton Hospital.
Sydney Street,
London, SW3 6NP

Email: brijesh.patel@imperial.ac.uk Email: romeo@imperial.ac.uk

Sponsor

Ruth Nicholson

Head of Research Governance and Integrity
Research Governance and Integrity Office
Imperial College London and Imperial College Healthcare NHS Trust
Level 5, 5th Floor, Sherfield Building, South Kensington Campus
Tel: + 44 20 7594 1862
E mail: r.nicholson@imperial.ac.uk

Clinical queries

Clinical queries should be directed to the Chief Investigator or ICTU Study Manager who will direct the query to the appropriate person.

Funders

National Institute for Health and Care Research (NIHR), Efficacy and Mechanism Evaluation (EME),
NIHR Coordinating Centre
University of Southampton, Alpha House,
Enterprise Road Southampton, SO16 7NS
Project Ref: NIHR158537

Tertiary Outcomes and Mechanistic Analyses funded via seed funding through our local charity (Royal Brompton & Harefield Charity).

ICTU Operations Management

Ms Hanna Box and Ms Mary Cross
Imperial Clinical Trials Unit (ICTU),
Imperial College London, School of Public Health
Stadium House, 68 Wood Lane, London, W12 7RH
Tel: +44 7715 631 551 (Hanna Box)

Tel: +44 7872 850 255 (Mary Cross)
Email: romeo@imperial.ac.uk

Study Manager

Dr Sharon Mumby
Cardiothoracic Advanced Life Support Laboratory,
Anaesthetics, Pain Medicine, and Intensive Care,
Chelsea & Westminster Hospital, Lift Bank D,
Fulham Road, London, SW10 6NP
Tel: +44 7355 611 894
Email: romeo@imperial.ac.uk

ICTU Study Monitor

Dr Ankita Duseja
Cardiothoracic Advanced Life Support Laboratory,
Anaesthetics, Pain Medicine, and Intensive Care,
Chelsea & Westminster Hospital, Lift Bank D,
Fulham Road, London, SW10 6NP
Tel: +44 7724 171 784
Email: romeo@imperial.ac.uk

Study Statisticians

Dr Leila Janani
Senior Statistician
Deputy Head of Trial Methodology
Imperial Clinical Trials Unit (ICTU),
Imperial College London, School of Public Health
Stadium House, 68 Wood Lane, London, W12 7RH
Tel: +44 20 7594 1737
Email: l.janani@imperial.ac.uk

Ms Lorna Hazell
Trial Statistician
Imperial Clinical Trials Unit (ICTU),
Imperial College London, School of Public Health
Stadium House, 68 Wood Lane, London, W12 7RH
Tel: + 44 7732 478 353
Email: l.hazell@imperial.ac.uk

Laboratories

Cardiothoracic Advanced Life Support Laboratory,
Anaesthetics, Pain Medicine, and Intensive Care,

Chelsea & Westminster Hospital, Lift Bank D,
Fulham Road, London, SW10 6NP
Email: romeo@imperial.ac.uk

Dr Sharon Mumby
Clinical Trial Manager
Senior Scientist
Tel: +44 7355 611 894
Email: s.mumby@imperial.ac.uk

Protocol development group

Professor Luigi Camporota
Professor Danny McAuley
Dr Leila Janani
Dr Michael Berry
Mrs Mary Cross
Professor Daniel Brodie
Professor Eddy Fan
Dr Richard Greendyke

In memory of Professor Luciano Gattinoni

Site Collaborators:
National ECMO Service Clinical Lead - Jo-anne Fowles
St Thomas' Hospital – Dr Patrick Collins, Prof Luigi Camporota
Royal Brompton Hospital – Dr Ben Garfield, Dr Jo Alcada, Mr George Georgovasilis
Royal Papworth Hospital – Dr Robert Gatherer
St Bartholemew's Hospital – Dr Sachin Shah, Dr Alastair Proudfoot, Debra Gaffney
Kings College Hospital – Dr Sam Patel, Dr Mike Berry
Bristol Royal Infirmary – Dr Stefan Gurney
Glenfield Hospital – Dr Hakeen Yusuff, Dr Vasileos Zochios
Wythenshaw Hospital – Dr Sam Howitt
Aberdeen Royal infirmary – Dr Callum Kaye, Dr Ian Scott

This protocol describes the ROMEO Trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other patients not in the trial; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination Centre (ICTU) to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination Centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
BPM	Breaths Per Minute
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ICU	Intensive Care Unit
IMV	Invasive-Mechanical Ventilation
ITT	Intention to Treat
LOS	Length of Stay
MP	Mechanical Power (of ventilator)
NAV	Near Apnoeic Ventilation
NIV	Non-Invasive Ventilation
PBW	Predicted Body Weight
PEEP	Positive End Expiratory Pressure
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGIT	Research Governance and Integrity Team (at Imperial)
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
VILI	Ventilator-Induced Lung Injury

TRIAL SUMMARY

TITLE: Rest Or Moderate mechanical ventilation during ECMO support

OBJECTIVES: To undertake a clinical efficacy study investigating near apnoeic ventilation (NAV) with two sigh breaths per minute after initiation of veno-venous Extracorporeal membrane oxygenation (VV-ECMO) for acute respiratory distress syndrome (ARDS), in comparison with standard ventilation of greater or equal to 10 breaths per minute.

DESIGN: This study is a two-arm, parallel-group, multi-centre, open-label, individually randomised controlled trial of rest or moderate mechanical ventilation on participants under ECMO support. It includes a 6-month internal pilot and is designed using a 3-stage group-sequential framework to allow for 2 interim analyses

SAMPLE SIZE: Initial aim to recruit 364 participants (182 in each arm) with a sample-size re-estimation planned at the second interim. This design allows for early stopping for futility and provides the opportunity to increase the sample size only if the interim results are promising.

INCLUSION/EXCLUSION CRITERIA:

i. Inclusion criteria

- Reversible cause of ARDS as determined by the treating physician prior to VV-ECMO cannulation
- Adult participants (18 years and over) undergoing invasive mechanical ventilation
- Requiring VV-ECMO for severe ARDS

ii. Exclusion criteria

- >48 hours from VV-ECMO initiation
- Participant likely to die or withdrawal of life sustaining therapy within 48 hours
- Bronchopleural fistula

INTERVENTION: *Near apnoeic ventilation strategy* will be set as follows: respiratory rate of two sigh breaths per minute. Each sigh breath will have a 30 cmH_2O plateau pressure (pressure control ventilation) for 3 seconds. Positive End Expiratory Pressure (PEEP) over the remaining 27 seconds will be set to maintain the same mean airway pressure obtained during the standardised ventilation pre-randomisation. FiO_2 will be set as low as possible provided that the SpO_2 >90%. These settings will be mandated for a minimum of 72 hours.

OUTCOME MEASURES

Primary Outcome

The primary outcome is the time from randomisation to successful decannulation from VV-ECMO (defined as 48 hours free of ECMO), incorporating death as a competing risk.

Secondary Outcomes

Secondary outcomes include the core outcomes defined for trials of mechanical ventilation and ECMO (1,2). These include:

- Days alive and free of ECMO (DAFE) up to day 28 and 60
- Daily Organ Support for participants on ECMO (DOSE) score up to 28 days post-randomization
- Mortality at 60 days, 6 months, and 1 year
- First successful liberation from invasive mechanical ventilation, i.e. > 48 hours of spontaneous ventilation (CPAP or HFNC)
- Duration of invasive mechanical ventilation
- Serious adverse events to hospital discharge (including AEs of specific interest related to NAV and ECMO - *as listed in Section 2 Objectives and Endpoints).*
- Length of total ICU and hospital stay
- Health-related quality of life (EQ-5D-5L) at 6 and 12 months

- Disability (Modified Rankin Scale) at 6 and 12 months

Tertiary mechanistic Outcomes (At appropriate sites)

1. Differences in bio-radiological markers (including but not limited to cytokine panel, single-cell and bulk RNA transcriptome, CT and metabolomic signatures) in broncho-alveolar lavage, bronchial brushing, plasma over time between assigned ventilation strategies.
2. Differences in lung mechanics (inspiratory capacity, transpulmonary pressure, recruitability), gas exchange, and haemodynamics over time between assigned ventilation strategies.

1 BACKGROUND

Acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome characterised by acute, diffuse, inflammatory lung injury resulting in hypoxaemic respiratory failure due to non-cardiogenic pulmonary oedema (3). ARDS occurs in response to a variety of insults, such as trauma, infections (e.g. pneumonia), sepsis, or pancreatitis. ARDS affects all age groups and is a major cause of short-term and long-term mortality of over 40% and causes a long-term reduction in quality of life for survivors (4,5). ARDS survivors experience exercise limitation, psychological sequelae, decreased physical quality of life, increased costs, and high use of health care services for up to 5 years after they recover from their acute illness (6). An international, multicentre, prospective cohort study in a convenience sample of 459 ICUs from 50 countries across 5 continents undergoing invasive mechanical (IMV) or non-invasive (NIV) ventilation reported a period prevalence of ARDS of 10.4% (29,144 admissions to 459 intensive care units from 50 countries) and 23% of patients requiring mechanical ventilation had ARDS (4).

Although lifesaving, mechanical ventilation can cause further injury to the lungs, known as ventilator-induced lung injury (VILI) (7). Strategies to mitigate VILI (including low tidal volume ventilation and prone positioning) in ARDS have demonstrated improvement in patient survival. Despite these lifesaving interventions, some ARDS patients continue to deteriorate and require veno-venous extracorporeal membrane oxygenation (VV-ECMO) (8). VV-ECMO involves the insertion of a large percutaneous venous access cannula to remove blood from the vena cava and pump blood through a membrane oxygenator, which takes over gas exchange. The oxygenated blood is then returned through a return cannula into the patient's central venous system. This enables controlling gas exchange and allows for significant reductions in ventilatory pressures and volumes thereby reducing the risk of VILI. Despite 50 years of research, there are no pharmacological therapies for ARDS and only supportive therapies exist enabling treatment of the underlying cause and prevention of VILI. The application of VV-ECMO support can supplement or supplant native lung gas exchange in ARDS, allowing reductions in the mechanical ventilatory forces contributing to VILI.

The positive impact of a protective lung ventilation strategy and VV-ECMO on survival in ARDS has been clearly demonstrated (9,10)). Patients supported on ECMO have the most severe form of ARDS and remain susceptible to VILI even with lower intensity breaths (11–13). Current evidence suggests using ventilatory strategies which reduce volumes and pressures for each breath delivered by the ventilator. Current evidence points towards utilising an ultra-protective ventilation strategy that limits tidal volume to <4 ml/kg PBW, targeting a low plateau pressure (<25 cmH_2O) alongside increased alveolar recruitment with PEEP is the current standard of care. However, significant uncertainty remains regarding the optimal management of mechanical ventilation in ECMO patients, as no prospective randomised clinical trial to date has assessed whether current lung-protective ventilation strategies are achieving maximal attenuation of VILI(14). As the application of ECMO increases internationally, future studies are urgently required to determine best ventilation practice in ARDS patients on ECMO with the aim to reduce ECMO duration, morbidity, and mortality.

It has been hypothesized that VILI depends on the amount of energy transferred to the patient's aerated lung parenchyma. Evidence shows that cumulative exposure to high intensities of mechanical ventilation as measured by ventilator mechanical power (MP) is a major determinant of VILI and mortality (15–17). A recent study showed that high mechanical ventilation power was independently associated with a higher in-hospital mortality rate in patients with ARDS (17). Thus,

lower MP means better prevention of VILI. MP is only modestly decreased by currently employed protective ventilation strategies which reduce predominantly tidal volume and plateau or driving pressure (18) but can be significantly reduced by lowering the respiratory rate (RR) (19). We hypothesise that an attenuation of MP with near apnoeic ventilation (or NAV) can lead to further improvements in clinical outcomes.

Proof of concept for near apnoeic ventilation (NAV) on ECMO. In patients with the severest forms of ARDS (at highest risk of VILI) requiring ECMO support, the maximal reduction in MP can only be achieved through a reduction in respiratory frequency (the greatest determinant of MP), thereby transferring total gas exchange to the membrane lung. Graf et al tested complete apnoeic ventilation (zero bpm) in 24 patients for 90 minutes and showed a significant reduction in stress, strain, and MP within the lung, which are important determinants of VILI (19). Sorbo et al performed a randomised physiological cross over study to and applied complete apnoea for 2 hours in 10 ARDS patients receiving ECMO and showed a linear reduction in the plasma concentration of biomarkers related to VILI (20). However, the application of complete apnoea in these physiological studies was tested over short periods (<2 hours). Learning from patients who have undergone one lung ventilation, it is well established that complete apnoeic ventilation is not recommended for a prolonged period (>24 hours) as it can lead to atelectasis and complete collapse of lung tissue. The resultant reduced lung compliance makes it more challenging to recruit and aerate lung regions when resuming mechanical ventilation and potentially increases the risk of VILI through excess regional lung strain when transitioning back to mechanical ventilation (21).
This has been well described in lung injury after one-lung ventilation for thoracic and oesophageal surgical procedures 22). In some cases, when mechanical ventilation is resumed, there may be a risk of excessive pressure settings causing barotrauma, especially if lung compliance has decreased during the period of apnoea. Complete apnoea can also lead to haemodynamic instability, particularly in patients with compromised cardiovascular function, which many patients on ECMO have. The reduction in intrathoracic pressure during complete apnoea impacts pulmonary blood flow and cardiac output through increased pulmonary vascular resistance and might precipitate right heart failure.

NAV intervention combining apnoea with two short cyclic recruitment manoeuvres (sigh breaths). NAV enables the greatest reduction in respiratory rate (RR) by combining evidence from two physiological concepts: 1) lung rest and 2) short cyclic alveolar recruitment manoeuvres (or “sigh” breaths) (23,24) The provision of two short cyclic recruitment manoeuvres (also known as sigh breaths) with periods of prolonged apnoea, will avoid complete lung collapse. Such sigh breaths have been shown to reduce regional lung strain through greater homogeneity in gas distribution within the ARDS lung. Ensuring the lung is kept open through cyclical sigh breaths VILI is further reduced by avoiding lung units inflating and deflating continuously. Indeed, two sigh breaths per minute (bpm) have been shown to avoid lung collapse and improve gas exchange capability in ARDS patients (23–25). This low respiratory rate with sigh breaths will maintain residual native lung gas exchange through avoidance of lung collapse (atelectasis) while achieving the closest and safest strategy to complete apnoea. In summary, the advantage of NAV is that it can allow a substantial reduction in mechanical power while maintaining alveolar recruitment (19,20,26). We hypothesise that this NAV strategy is associated with faster lung recovery with an associated reduction in duration of ECMO, ventilation and ICU stay.

Current standard of care. We conducted a search of PubMed, Ovid, Cochrane databases, and International Clinical Trials Registries to outline the current state of knowledge and activity in this area. There remains uncertainty as to the best approach to mechanical ventilation whilst patients are receiving ECMO and whether we are maximally attenuating VILI during ECMO use. Most patients on ECMO continue to have 10-30 breaths delivered per minute by the ventilator and this may be causing harm. It is important to appreciate that each 10 breaths per minutes extrapolates to an additional 100000 breaths per week. There are numerous review articles with respect to mechanical ventilation on ECMO support. The LifeGARDS study was a multinational survey of mechanical ventilation during ECMO support and showed significant variations in standard practice with 45.7% of centres using a moderate RR (10-20 breaths per minute, bpm) each delivering ~10-

15 cmH_2O PEEP and 10-15 cmH_2O driving pressure (27). The RR used in the most recent RCT in VV-ECMO showed a rate of 10-30 breaths per minute (28). The standard management in the UK is less heterogenous than the global data with our survey (conducted in response to committee feedback) showing 20/22 respondents using 10-15 bpm and 2/22 using 16-20 bpm across all UK sites.

In the UK, ECMO for severe acute respiratory failure has been provided nationally as a highly specialist commissioned service since 2010, with nearly 3000 patients receiving ECMO since 2015 in the UK. The UK ECMO network published a description of the patients managed between 2011 and 2018, and despite the high severity of illness represented in this cohort, the overall outcomes were very good with 887/1205 (74%) patients surviving discharge from the ECMO IC (29). The criteria for ECMO initiation are standardised in the UK and ECMO utilisation is increasing (30,31). The impact of requiring ECMO is significant in terms of ICU morbidity and healthcare costs, hence, any improvement in management leading to reduced ECMO duration would have great impact on practice and outcomes. Severe ARDS patients have a median (inter-quartile range (IQR)) duration of mechanical ventilation of 9(4-16) days, ICU length of stay of (LOS) of 11(5-19) days, and hospital LOS of 16(6-31) days. In contrast, very severe ARDS patients supported with ECMO show a median (inter-quartile range (IQR)) duration of mechanical ventilation of 18(11-24) days within which duration of ECMO is 12(8-24) days. Overall, ICU length of stay of (LOS) is 24(14-39) and hospital LOS is 35(20-55) days. Patients with ARDS supported on ECMO utilise considerable ECMO unit capacity and cost (cost per NHS ECMO bed-day = £5421 versus that of ICU bed-day = £816-2011). The mean estimated cost of ICU stay based on a UK RCT involving ARDS patients was £26,857 (95 % CI £25,222–£28,491). The CESAR study (which led to the national commissioning of ECMO) showed mean healthcare costs per ARDS patient were more than twice as high for patients allocated to consideration for treatment by ECMO as compared to those allocated to conventional management. The mean difference in costs were £40,544. Hence, the utilisation of ECMO leads not only to a significantly greater patient morbidity (due to increased ICU LoS) but also a greater burden on healthcare resources. Thus, improvement in management leading to reduced ECMO duration would have great impact on practice and outcomes.

2 OBJECTIVES AND ENDPOINTS

Primary Objective

To undertake a clinical efficacy study investigating near apnoeic ventilation (NAV) with two sigh breaths per minute after initiation of veno-venous Extracorporeal membrane oxygenation (VV-ECMO) for acute respiratory distress syndrome (ARDS), in comparison with standard ventilation with respiratory rate greater or equal to 10 breaths per minute.

Secondary Objectives

Determine the impact of NAV on several short and long-term participant related outcome measures.

Tertiary Objectives

Pathobiological and physiological mechanistic evaluation of differential treatment effect of near-apnoeic ventilation through analysis of biological samples (blood, bronchoalveolar lavage, and bronchial brushings) and analysis of granular physiological measurements.

Primary Outcome

The primary outcome is the time from randomisation to successful decannulation from VV-ECMO (defined as 48 hours free of ECMO), incorporating death as a competing risk.

Secondary Outcomes

Secondary outcomes represent the core outcomes defined for trials of mechanical ventilation and ECMO (1,2). These include:

- Days alive and free of ECMO (DAFE) up to day 28 and 60

- Daily Organ Support for participants on ECMO (DOSE) score up to 28 days post-randomization
- Mortality at 60 days, 6 months, and 1 year
- First successful liberation from invasive mechanical ventilation, i.e. > 48 hours of spontaneous ventilation (CPAP or HFNC)
- Duration of invasive mechanical ventilation
- Serious adverse events to hospital discharge (including AEs of specific interest related to NAV and ECMO as listed below)
- Length of total ICU and hospital stay
- Health-related quality of life (EQ-5D-5L) at 6 and 12 months
- Disability (Modified Rankin Scale) at 6 and 12 months

List of AEs of specific interest

NAV related

- Refractory hypercapnia (pH <7.25 despite maximal ECMO management)

ECMO related

- International Society on Thrombosis and Haemostasis (ISTH) defined major bleeding (fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more or leading to a transfusion of 2 U or more of whole blood or red cells.)
- New DVT, pulmonary embolism, thrombotic stroke
- Intracranial haemorrhage

Tertiary Mechanistic Outcomes (At appropriate sites)

- Differences in bio-radiological markers (including but not limited to cytokine panel, single-cell and bulk RNA transcriptome, CT and metabolomic signatures) in broncho-alveolar lavage, bronchial brushing, plasma over time between assigned ventilation strategies.
- Differences in lung mechanics (inspiratory capacity, transpulmonary pressure, recruitability), gas exchange, and haemodynamics over time between assigned ventilation strategies.

3 STUDY DESIGN

This study is a two-arm, parallel-group, multi-centre, open-label, individually randomised controlled trial of rest or moderate mechanical ventilation on patients under ECMO support, with a 6-month internal pilot to monitor screening and recruitment.

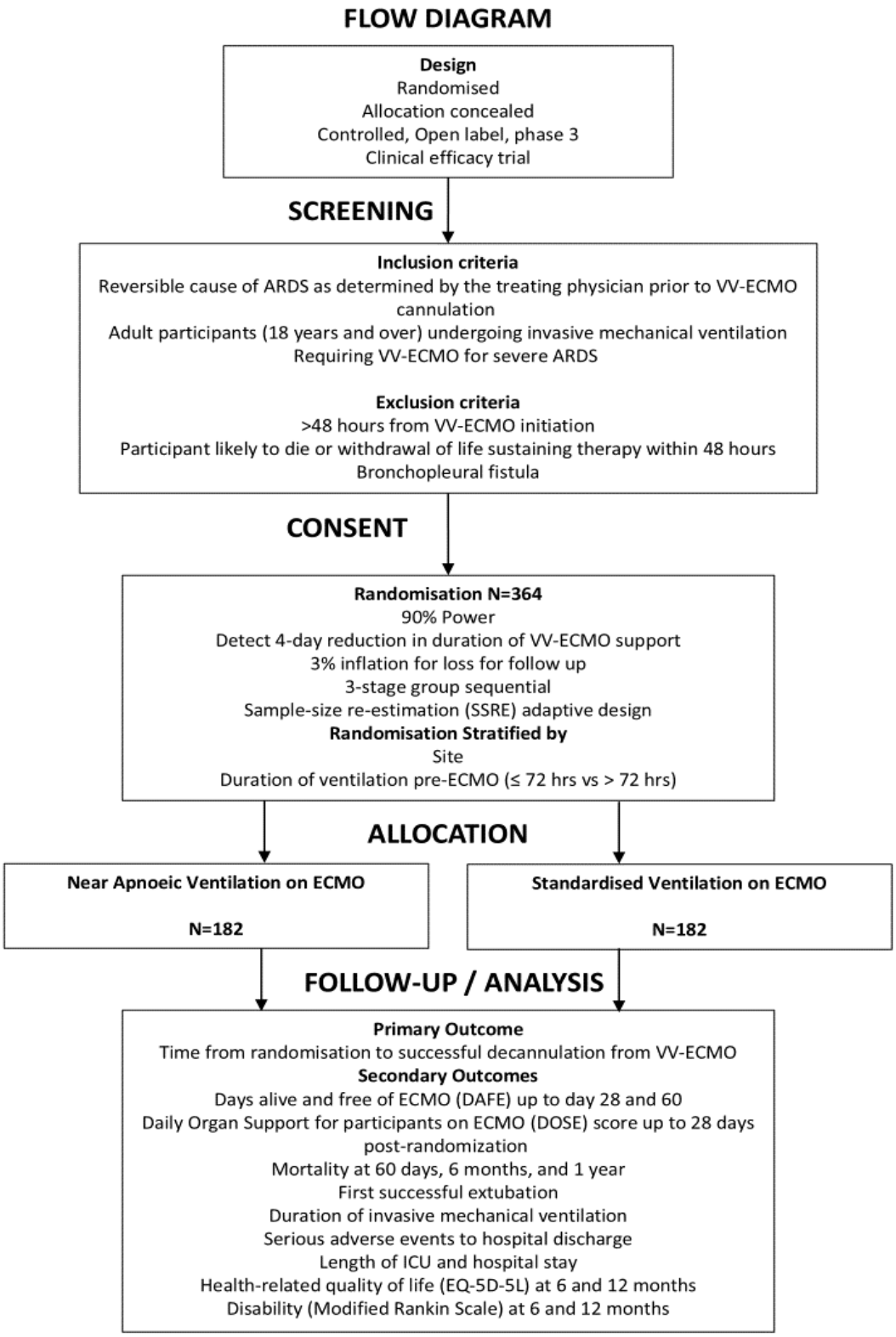
It follows a 3-stage group-sequential design with 2 pre-planned interim analyses at 40% and 60% of the observed events, and a sample-size re-estimation planned at the second interim. This design allows for early stopping for futility and provides the opportunity to increase the sample size only if the interim results are promising.

The trial will be performed at 9 ECMO sites in the UK. Eligible participants will be randomised to two ventilation strategies – near apnoeic ventilation with 2 sigh breaths vs standard ventilation with ultraprotective tidal volumes and 10 or more breaths per minute.
Enrolment and allocation to treatment arms will be performed using a secured online system.

Internal Pilot

We include an internal pilot study to assess recruitment. This will run for the initial 6 months of recruitment and run seamlessly into the main trial, if the success criteria are met (see Section 8). The internal pilot report will be submitted to NIHR following discussion with TSC and DMC.

Study Flow Chart



4 PARTICIPANT ENTRY

Study setting and population

The target population is adult participants with ARDS (as defined by Berlin criteria) requiring VV-ECMO support admitted to sites in the NHS England Commissioned Network for VV-ECMO.

i) Inclusion criteria

- Reversible cause of ARDS as determined by the treating physician prior to VV-ECMO cannulation
- Adult participants (18 years and over) undergoing invasive mechanical ventilation
- Requiring VV-ECMO for severe ARDS

Within the context of this study, 'ARDS' will be defined using the Berlin definition criteria (32) applied prior to ECMO cannulation:

- Symptoms must appear within one week of a known clinical event or worsen within that time
- Chest x-ray or CT scan must show bilateral opacities that aren't fully explained by other factors
- Respiratory failure can't be caused by cardiac failure or fluid overload
- The ratio of partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspired oxygen (FiO2) determines the severity of ARDS:
  - Mild ARDS: PaO_2/FiO_2 of 200-300mmHg / 27-40 kPa
  - Moderate ARDS: PaO_2/FiO_2 of 100-200mmHg / 13-27 kPa
  - Severe ARDS: PaO_2/FiO_2 less than 100mmHg / 13 kPa

ii) Exclusion criteria

- >48 hours from VV-ECMO initiation
- Participant likely to die or withdrawal of life sustaining therapy within 48 hours
- Bronchopleural fistula

Patients are potentially eligible for co-enrolment in other studies, this will be decided on a case-by-case basis in keeping with UK guidelines for critical care research. Imperial Clinical Trials Unit (ICTU) and the CI should be informed if co-enrolment is being considered. Co-enrolment with any studies should be documented in the CRF.

5 PROCEDURES AND MEASUREMENTS

Identification and recruitment of participants

Participants will be identified by local clinical and clinical research staff employed in the recruiting hospitals.

No additional tests or data are required for screening to assess eligibility for the trial. The screening will be conducted by local clinical and clinical research staff employed in the recruiting ECMO ICUs, using the routinely clinically collected data.

Screening and pre-randomisation evaluations

Written informed consent will be obtained before the participant undergoes randomisation. Where the patient lacks capacity consent will be gained from a Personal Legal Representative or Professional Legal Representative. For **sites in Scotland** consent will be gained from a Welfare Attorney/Welfare Guardian/Nearest relative.

Randomisation and Blinding

Adult participants diagnosed with ARDS and receiving support from both a ventilator and ECMO machine will undergo eligibility screening. Those deemed eligible and who provide consent either personally or (**for sites in England**) through a legal representative or (**for sites in Scotland**) Welfare Attorney/Welfare Guardian/Nearest Relative will be randomly assigned to receive either conventional mechanical ventilation or near-apnoeic ventilation (NAV). The randomisation process will be conducted through a web-based system (OpenClinica – Sealed Envelope), utilising a stratified permuted block design. Stratification will be based on the site of recruitment and the duration of invasive mechanical ventilation pre-ECMO (≤ 72 hrs vs > 72 hrs).

Concealment will be achieved through use of an online system – this will be using Sealed Envelope through the study specific OpenClinica database/eCRF.

The NAV intervention is open-label whereby the clinical team and study team will not be masked. We aim to minimise bias using time from randomisation to decannulation from VV-ECMO as an objective primary outcome, as well as DAFE and DOSE as secondary outcome measures. No aggregated data by arm will be available to the study team throughout the trial.

Visit Schedule

Please refer to Appendix 1.

Follow-up

Participants will be followed up by the clinical research team daily whilst in ICU. Once the participants have left the ECMO ICU and been discharged to the referring hospital, they will be followed up prior to hospital discharge from the referring hospital. Follow-up at 6 and 12 months will be via either electronic/postal/telephone questionnaires, medical records and data linkage with NHS Digital (eDRIS in Scotland) records wherever possible.

Exploratory Biological and Physiological Evaluations

Please see Appendix 2 for ROMEO Physiology and ROMEO Biology data/sample collection.

6 INTERVENTION

This trial assesses a process of care which involves a near apnoeic ventilation strategy in participants undergoing invasive mechanical ventilation already supported with ECMO. Cross-over is very unlikely but cannot be ruled out. If it were to occur the patient would remain in the study.. This will be monitored during the trial and re-training provided if required. The intervention will be ongoing until the following:

- Treating physician changes ventilation settings.
- Death.
- Request to withdraw from the study.
- Treating physician withdraws the patient from the study based on safety.
- Successful unassisted breathing., i.e. > 48 hours of spontaneous ventilation (CPAP or HFNC)

We will implement a standardised management protocol consistent with best evidence from the recent EOLIA Trial (see control arm strategy below) (28).
Our standardised management will include:
After consent and prior to randomisation: Consented participants will be ventilated prior to randomisation as per usual care within the ECMO unit. We will document mean airway pressure and number of days ventilated prior to randomisation.
After randomisation to the:

Control arm of usual care, ventilation will be set as follows: pressure control ventilation with at least 10 breaths/min and a plateau pressure ~25 cmH_2O with PEEP of ~10 cmH_2O and an

I:E 1:1 to 1:2 and a tidal volume of 3-6mL/kg. FiO_2 will be set as low as possible provided that SpO_2 >90%. These settings will be maintained for a minimum of 72 hours (day 1-3).

Intervention arm of near apnoeic ventilation strategy, ventilation will be set as follows: respiratory rate of two sigh breaths per minute. Each sigh breath will have a 30 cmH_2O plateau pressure (pressure control ventilation) for 3 seconds. PEEP over the remaining 27 seconds will be set to maintain the same mean airway pressure obtained during the standardised ventilation pre-randomisation. FiO_2 will be set as low as possible provided that the SpO_2 >90%. These settings will be mandated for a minimum of 72 hours (day 1-3).
Beyond 72 hours, the daily management of the ventilator and ECMO will be based on clinical study-specific procedure manuals and advice to continue NAV intervention will be given until the participant meets the following "improvement criteria":

- Radiological/clinical improvement
- Tidal volume (VT) of ≥4-6 mL/kg predicted body weight with PEEP and driving pressure ≤15 cmH_2O with PaO_2 >30kPa on FiO_2 1.0.

ECMO Strategy: The extracorporeal support will be set as follows: ECMO blood flow >3 L/min, ECMO gas flow as required to maintain arterial $PaCO_2$ <8kPa. Higher blood flow alongside cardiac output suppression (as per site usual practices) will be provided in the case of severe hypoxemia (PaO_2<60 mmHg or 8 kPa). The management of ECMO targets will be protocolised to ensure prevention of cross-over between arms.

Permanent Discontinuation of Study Intervention and Withdrawal from Study

i) Permanent discontinuation of study intervention

Participants may discontinue study intervention but continue with other study procedures (e.g. biological sampling) for the following reasons:

- At the request of the participant or **(for sites in England)** participants representative (**for sites in Scotland)** the Welfare Attorney/Welfare Guardian/Nearest Relative.
- Adverse event/ Serious Adverse Event
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study intervention and all study procedures (including any biological sampling) and can occur for the following reasons:

- Participant decision or **(for sites in England)** participants representative (**for sites in Scotland)** the Welfare Attorney/Welfare Guardian/Nearest Relative.
- Loss to follow-up

iii) Procedures for Withdrawal from Study

Participants will be free to withdraw at any time. If the participant (or their personal/professional legal representative **or for sites in** Scotland the Welfare Attorney/Welfare Guardian/Nearest Relative wishes to withdraw from the study during the treatment period the treating physician will no longer follow the trial protocol, and the intervention and all study procedures will be stopped. If the participant withdraws from the study this will be documented in the eCRF and medical records.

The participant will be able to either withdraw completely from the trial (withdraw from study) or from certain elements. If the participant withdraws fully from the study all further follow-up visits as part of the clinical trial will cease. However, the participant will be asked if data collection through data linkage using NHS Digital (eDRIS in Scotland) of routinely collected data, including long-term follow-up can continue.
Already collected data will not be deleted as these will include important safety information which would be processed as part of a legitimate interest.

If participants withdraw completely from the study any previously collected, stored biological samples will be used but no further samples will be collected.

7 SAFETY REPORTING

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a trial intervention and which does not necessarily have a causal relationship with this intervention / treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial intervention, whether or not considered related.

Adverse Event recording

As this is a trial conducted in critically ill patients with life-threatening critical illness then Adverse Events (AEs)/Reactions (ARs) are expected to occur regularly in most, if not all, patients. Therefore, unless an adverse event is assessed to meet Serious Adverse Event (SAE) criteria or is an AE of specific interest (as listed below), these adverse events will not be reported in the case report form (CRF) and simply noted in the patient's local medical record. Any clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the local investigator.

i) List of AEs of specific interest

NAV related

- Refractory hypercapnia (pH <7.25 despite maximal ECMO management)

ECMO related

- International Society on Thrombosis and Haemostasis (ISTH) defined major bleeding (fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of 2 U or more of whole blood or red cells) (33).
- New DVT, pulmonary embolism, thrombotic stroke

ii) Severity of Adverse Events

Definitions for assessment of severity:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

iii) Causality of Adverse Events

If any doubt about the causality (in relation to the intervention) exists, the local investigator should inform the Trial Coordination Centre who will notify the Chief Investigator. Other clinicians may be asked to advise in some cases. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case.

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another

reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Serious Adverse Events (SAE)

i) Definition of SAE

An SAE is defined as any event that
- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

ii) Reporting of SAEs

As the secondary outcome of the trial includes mortality, then death does not require reporting as an SAE unless, in the opinion of the local PI, the death was attributable to the study intervention or the trial protocol. Similarly, the secondary outcomes have been selected to capture the most commonly occurring serious adverse events (including AEs of specific interest related to NAV and ECMO). Therefore, any events that are captured as an outcome in the eCRF do not require reporting as an SAE unless in the opinion of the local PI the event was attributable to the study intervention or the trial protocol.

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the participant's ICU stay must be performed as detailed in the study-specific safety reporting instructions. Active monitoring of participants after discharge from ICU is not possible, but if the investigator becomes aware of safety information that appears to be trial related, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed on the OpenClinica database by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (eCRF):

iii) Related SAEs

Related: resulted from administration of any of the research procedures (where causality is assessed as possible, probable or definite).

iv) Unexpected SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence.

v) Reporting of SAEs that are related and unexpected

SAEs that are *related and unexpected* should be notified to the relevant REC and the Sponsor in accordance with local requirements. For Imperial-Sponsored studies, related and unexpected SAEs must be reported to the Sponsor within 15 days of the investigator becoming aware of the event.

Follow up of participants who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised.

Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than three days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

8 STATISTICS AND DATA ANALYSES

Sample Size and power considerations

The primary outcome of this trial is time from randomisation to successful decannulation from VV-ECMO. We will undertake a 3-stage group-sequential design [with 2 interims planned at 40% and 60% of the observed events and one final analysis], which will allow us to stop early for futility, thereby increasing the statistical efficiency of the trial. We require a total of 269 events [successful decannulation from ECMO] to achieve a 90% power at a one-sided type I error rate of 2.5% to detect a 4-day reduction in the median time to decannulation from ECMO (assuming 12 days in the control group) and accounting for death as a competing risk. To achieve this, our study necessitates the inclusion of 352 subjects.
Considering a potential 3% dropout rate, our goal is to recruit 364 participants (182 per arm).
As the sample size calculation for a group-sequential design with a time-to-event outcome in the presence of competing risk is not straightforward; we followed the below steps for calculations.

- By choosing cause-specific hazard model (CSH) as a primary analysis approach, we calculated the sample size for a fixed design in the presence of competing risks using the "Logrank Tests Accounting for Competing Risks" procedure in PASS 2022. Considering that decannulation from ECMO is a positive outcome, a 4-day reduction in median time equates to a hazard ratio of 1.5 (a higher rate of decannulation in favour of the intervention arm), and assuming a 70% event (successful decannulation) rate by 60 days, a 26% death rate (competing event) in the control group, and a 39-month recruitment time with a 12-month follow-up, we need 257 events (336 participants) to achieve 90% power at a one-sided type I error rate of 2.5%.

- In the next step, we employed the gsDesign package within R software version 4.3.0 to create a 3-stage group sequential design with planned interim analyses at 40% and 60% of observed events, integrating non-binding futility boundaries using the Lan-DeMets O'Brien-Fleming approximation spending function. We will need 269 events (352 participants) to

achieve 90% power. It's worth noting that due to the potential for early termination due to futility, the expected number of events is now 210.
Table 1 provides the futility boundaries for each stage of analysis

Table 1: Futility boundaries by analysis stage

Stage	I	II	III
% of total events at Interim	40%	60%	100%
Number of events across both arms	108	162	269
Z score for lower futility boundary	-0.26	0.70	-

The sample size estimation was then validated using code developed by an independent statistician at ICTU. The required number of events was calculated using the **rpact R package approach**, yielding a total of 268 events. Given the presence of competing risks, the required number of participants was adjusted using the formulas provided in the **PASS documentation**, resulting in a final sample size of 350, which aligns with the original calculations.

Internal Pilot:

Data will be analysed at the end of the internal pilot stage (months 7–12), based on patients recruited during the first 6 months of the trial. The analysis will be conducted in month 13 to allow sufficient time for data collection and entry, enabling a complete assessment of all progression criteria and minimising missing data.

The objectives of the internal pilot analysis are to assess whether site set-up, screening, and recruitment have been successful. Progression from the pilot stage to the full trial will be determined based on predefined progression criteria.

If any of the progression criteria are rated as 'Amber' or 'Red' a management plan will be developed by the Trial Management Group and discussed with the Trial Steering Committee. The final decision on whether the trial progresses to the full phase will be made by the NIHR EME Programme, following a recommendation from the TSC.

A traffic light system will be used to assess progression from the pilot stage to the full trial, as outlined below:

Criterion	**Green light (Progress to the main trial)**	**Amber light (Explore methods to improve domain criteria)**	**Red light (Discuss with funder)**
Number of sites open to recruitment	9/10* (100%)	5 to 8/9 (50 – 80%)	<5 (<50%)
Number of patients enrolled	30 (100%)	19 to 29 (60-99.99%)	<18 (<60%)

*The 10th centre is a hibernating centre only activated during winter surge and pandemics.

In the internal pilot, the TSC will also informally monitor measures of adherence:

- Average separation in respiratory rate between NAV and standard care

- Days of NAV
- Number of protocol violations i.e. cessation of NAV

Planned recruitment rate

A recruitment window of 39 months covers 3 full winter seasons, optimising capability for enrolment whilst enabling time for optimal set-up and 1-year follow up. This gives a total pool of ca. 1000 patients across 9 ECMO centres. Regular assessments taking into consideration the seasonal variation of ECMO activity will ensure engagement with the trial at each site to ensure optimisation of recruitment. Furthermore, regular study updates with clinical and research leads will be communicated during already established national network calls (weekly during winter surge; monthly at other times) and 6 monthly network meetings.
There are no other national studies in the UK network which would impact this study. Going forward, we will ensure we bring on ECMO ICUs that have not traditionally participated in research, in particular newer centres, to directly address the Levelling up Heath agenda and NIHR's INCLUDE programme. There is geographic diversity in ECMO service provision, and this reflects a population exposure and the burden of disease of ARDS as well as including communities which are often traditionally underserved in research. For instance, the population from the devolved nations of Wales and Northern Ireland are served by the NHS England centres.

Statistical Analysis

A Statistical Analysis Plan (SAP) will be prepared, detailing all analyses included in the trial, along with model specifications and statistical code. The SAP will be finalised and approved before the first planned interim analysis. Any deviations from the SAP will be documented and justified in the final report.
The participant flow through the trial and trial results will be reported following the CONSORT Extension for Adaptive Designs (ACE) guidelines (34).
Baseline characteristics will be presented by study arm and overall, using appropriate measures of central tendency and dispersion. For continuous data, this includes means and standard deviation (SD) or median and interquartile range (IQR). For categorical data, frequencies and proportions will be provided. Both Kaplan-Meier and Aalen and Johansen (35–37) estimators will be employed to estimate the time from randomisation to decannulation from ECMO distribution and the resulting distributions will be graphically presented for each treatment group.

Interim Analysis

We have scheduled two formal interim analyses to assess futility when approximately 40% and 60% of the planned number of events (successful decannulation from ECMO) are available. The study is designed with a non-binding futility boundary using the Lan-DeMets O'Brien-Fleming approximation spending function.

Following the recommendation by Baayen et al. (38), we intend to present results from both cause specific hazard (CSH) and cumulative incidence (CI), of the sub-divided distribution models, to the Data Monitoring Committee (DMC) for their consideration. By presenting results from both common approaches for the analysis of competing risk data and incorporating non-binding boundaries, we provide the DMC with comprehensive information and give them flexibility in incorporating supplementary information when making decisions regarding potential early termination.

We will use the results from the **second interim analysis** (at **60% of events**) to **re-evaluate the sample size** and assess the **possibility of increasing it**. The **conditional power (CP) approach** will be used, and if the estimated CP is at least 60%, we will consider increasing the sample size to the maximum feasible amount of 550 participants. The **60% cut-off** was chosen based on **initial simulations** conducted by the **independent statistician**, which indicated that this threshold would **preserve the trial's operating characteristics** while maintaining the planned **alpha level of 2.5% and beta level of 10%**.

Given the **complexity of the trial design**, which incorporates a **group sequential approach for competing risks**, we plan to conduct **additional simulations**. Further details on the **decision rules** will be outlined in the **SAP**.

The **DMC** will review the interim data and make **recommendations to the TSC** regarding **any safety or futility concerns** that may warrant stopping the trial. The trial will continue **recruiting participants while the interim analyses are conducted**.

None of the interim analysis results will be shared with the investigators prior to the completion of the trial. Additionally, regular safety analyses will be performed (approximately 6 monthly) and results will be reviewed by the DMC.

Analysis populations

The primary analysis population will be the intention to treat (ITT) population, including all participants who undergo randomisation will be analysed in their assigned arms, regardless of what they receive. Participants or their personal/professional legal representative or **for sites in Scotland** the Welfare Attorney/Welfare Guardian/Nearest Relative who withdraw from the trial will be included in the analysis unless they withdraw their consent. If consent is withdrawn data up to the point of withdrawal will be included in the data analysis.

Primary Endpoint Analysis

Primary Estimand: Time to successful decannulation from ECMO is defined as the time between the date of randomisation and the date of successful decannulation or the date of the last follow-up whichever, earliest. The primary research question aims to investigate whether the use of near-apnoeic ventilation (NAV) with two sigh breaths per minute after the initiation of ECMO is superior to the standard lung-protective ventilation of at least 10 breaths per minute in patients diagnosed with ARDS and receiving support from both a ventilator and ECMO machine.
In addressing this question, considering the crossover between study arms and death as potential intercurrent events, the primary estimand is defined as follows:

- **Population**: Adult patients diagnosed with ARDS and receiving support from both a ventilator and ECMO machine and meet trial eligibility criteria
- **Treatment:** Near apnoeic ventilation (NAV) with two sigh breaths per minute vs standard lung protective ventilation of at least 10 breaths per minute (SOC).
- **Variable**: Time from randomisation to successful decannulation from ECMO
- **Population-level summar**y: Cause-specific hazard ratio of NAV vs SOC
- **Intercurrent events**: Crossover between study arms and death

Intercurrent Events	Strategy for handling Intercurrent Events in the analysis
Crossover between study arms	Treatment policy strategy: using time to successful decannulation from ECMO, regardless of whether crossover between arms had occurred.
Death	Hypothetical strategy: using a cause-specific hazard model in which death will be treated as a competing risk for the successful decannulation from ECMO

There are two statistical approaches to consider competing risks: the **cause-specific hazard (CSH)** and **cumulative incidence (CI)**, also known as the **sub-divided distribution** approach. Each approach has its own advantages and limitations, effectively complementing one another but answering different questions. In this study, where decannulation is considered as a positive event and death as a competing negative event, our primary statistical method will involve the use of a Cox model to estimate the **cause-specific hazard rate ratio**. This approach enables us to estimate the probability of a patient's decannulation from ECMO in the immediate future, given their current

state of being alive and on ECMO at a specific time point. This aligns with the hypothetical strategy for handling death and, regardless of any crossover between study arms, and remains consistent with the treatment policy approach in case of crossover between arms.

Time to decannulation from ECMO will be censored at the point of withdrawal or loss to follow-up, and withdrawals will be assumed to lead to missing at random (MAR) data on the primary outcome. The primary analysis will be adjusted for stratification variables and the results will be presented in terms of hazard ratios (HRs) accompanied by their corresponding 95% confidence intervals and p-values. We will add the duration of ventilation pre-ECMO (≤ 72 hrs vs > 72 hrs) as a fixed effect to the primary model and recruitment site will be included as a random effect by incorporating frailty unless there are fewer than expected sites or another reason to model site as a fixed effect.

Supplementary Estimands and Analyses:
Three supplementary estimands and analyses are defined to support the primary estimand and analysis.

- **Supplementary Estimand 1**: A supplementary analysis will be undertaken, employing a composite strategy to handle death using cumulative incidence (CI) approach and a Fine and Gray proportional sub-distribution hazards model. This estimand will explore how the treatment affects the likelihood of a participant being decannulated from ECMO within a specific number of days while still considering participants who died as potentially at risk for decannulation.
- **Supplementary Estimand 2**: A supplementary analysis will be undertaken, employing a hypothetical strategy to handle crossover between arms. This estimand will explore the treatment effect if all participants had continued treatment as planned and had not had any subsequent switching between study arms. Under this estimand time to successful decannulation from ECMO will be censored at the time of crossover between study arms, and inverse probability of [not] censoring weighting (IPCW) will be used to estimate the cause-specific hazard ratios (HRs) using the same analysis model described for the primary estimand.
- **Supplementary Bayesian Analysis**: A supplementary analysis will be undertaken, employing a Bayesian approach. This involves a Bayesian competing risk model with non-informative and informative priors, dependent on the data available at that time. This approach enables us to interpret results in terms of the probability of superiority for various reductions in median time to decannulation (e.g., 2 days, 3 days, and 4 days), moving beyond traditional hypothesis testing and a binary decision (significant or non-significant).

Sensitivity Analysis:
The proportional cause-specific hazard assumptions of the Cox model will be evaluated through the analysis of Schoenfeld residuals. In the event of any violations from the proportionality assumption, a Stratified Lunn-McNeil model will be applied to estimate cause-specific hazard ratios.
We will also incorporate multi-state model to estimate cause-specific hazard ratio with considering the following states:

- On ECMO (Initial State)
- Decannulation (Recovery/Positive Outcome)
- Death (Competing Event/Negative Outcome)

Secondary Endpoints Analysis

For binary outcomes (e.g. Mortality at 60 days, 6 months, and 1 year) we will use log-binomial model with a fixed effect for the duration of ventilation pre-ECMO (≤ 72 hrs vs > 72 hrs) and a random effect for study site (as a random intercept) to estimate an adjusted Risk Ratio with a 95% confidence interval and p-value. If there is a convergence problem with the log-binomial model, Poisson regression with robust standard errors (modified Poisson regression) will be used. We will

use the same approach described in the primary analysis to estimate hazard ratios and corresponding 95% CIs for time-to-event outcomes. For the **DOSE score**, a longitudinal ordinal outcome assessed daily to day 28, we will use **mixed-effects ordinal logistic regression to estimate** Cumulative odds ratio.

Adjusted analysis

Primary and secondary endpoints analyses will be adjusted for stratification variables, including a **fixed effect** for the duration of ventilation pre-ECMO (≤72 hours vs >72 hours) and a **random effect** for the study site (as a random intercept).

Safety Analysis

The safety population for the analysis of adverse events will consist of all randomised participants except for participants who withdraw consent to use their data in the trial. Adverse events will be coded using the MedDRA dictionary. We will report the total number of adverse events in each arm, as well as the number of patients who experienced at least one adverse event in each treatment group. Clinical adverse events will be summarised at the System Organ Class level, and descriptive statistical methods will be supplemented by estimating the Incidence Rate Ratio and plotting with 95% CIs.

9 REGULATORY, ETHICAL AND LEGAL ISSUES

Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the most recent revision of the 1964 Declaration of Helsinki.

Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

Research Ethics Committee (REC) Approval

Initial Approval

Prior to the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form and any other written information that will be provided to the participants.

Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Amendments to the protocol will be decided by the Chief Investigator and the Protocol Development Group and will be submitted to the Imperial College London Research Governance and Integrity Team for review prior to submission. Whether the changes in the protocol are substantial, or non-substantial will be guided by the amendment tool as provided by the HRA/REC. An updated version and date of the protocol will be documented in the title and footer of the document, the approval pack (containing the updated protocol) will also be sent to all participating sites for local approval prior to implementation.

End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

The end of trial notification will be submitted within 90 days of the end of trial definition being met. This clinical study will end when the specified number of participants have been recruited all participants have completed their 12-month follow-up and the database is hard locked.,
In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU Head of QA on a monthly basis. Protocol violations will be reported to the Sponsor.
An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.
A serious breach is defined as:
A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

Insurance and Indemnity and Sponsor

The Sponsor has civil liability insurance, which covers this study in all participating countries. Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

Trial Registration

The study will be registered on a trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations. The study will be registered on the ISRCTN registry.

Informed Consent

For sites in England: It will not be possible to gain prospective consent for the participant at the time of enrolment due to their state of severe critical illness. Consent will be obtained as soon as possible from the participant's Legal Representative, where patients lack capacity due to the nature of their critical illness or effects of sedation. In most cases this person will be a personal legal representative (PerLR), who is someone who knows the person lacking capacity and is able to advise the researcher about that person's wishes and feelings in relation to the study and whether they should participate in the research. This person must be interested in the welfare of the patient in a personal capacity, not in a professional capacity or for remuneration and will most likely be next of kin (NOK). Consent from the personal legal representative (PerLR) will be sought as soon as possible. If the PerLR is not able to attend in person, the research team will contact them via telephone call and/or online via videocall and consent will be obtained verbally using a remote

declaration form, in the presence of a second witness. The PerLR identity will be verified via a video link or other means, in line with the methods used by the clinical team to update family member / NOK about the clinical management of the participant.
If a family member/NOK is not available a doctor who is not part of the study (i.e. not on the trial research delegation log) will be approached to give their professional legal representative (ProLR) consent. This would usually be a senior treating clinician of the patient.
Once the participant regains capacity, they will be approached to provide their retrospective consent to remain in the study.

For sites in Scotland: It will not be possible to gain prospective consent for the participant at the time of enrolment due to their state of severe critical illness. Consent will be obtained as soon as possible from the participant's Welfare Attorney/Welfare Guardian/Nearest Relative, where patients are adults with incapacity due to the nature of their critical illness or effects of sedation. The Welfare Attorney/Welfare Guardian/Nearest Relative should be someone who knows the person lacking capacity and is able to advise the researcher about that person's wishes and feelings in relation to the project and whether they should participate in the research. This person must be interested in the welfare of the patient in a personal capacity, not in a professional capacity or for remuneration. If the Welfare Attorney/Welfare Guardian/Nearest Relative is not able to attend in person, the research team will contact them via telephone call and/or online via videocall and consent will be obtained remotely, in the presence of a second witness. The Welfare Attorney/Welfare Guardian/Nearest Relative identity will be verified via a video link or other means, in line with the methods used by the clinical team to update a family member about the clinical management of the participant.
Once the participant recovers capacity, they will be approached to provide their retrospective consent to remain in the study.

Further, we will adopt the INCLUDE Impaired Capacity to Consent and Ethnicity Frameworks being developed by the MRC-NIHR Trial Methodology Research Partnership. Our trial will be an early adopter of this framework that aims to enhance research inclusion for patients with impaired mental capacity and will collect appropriate data (e.g., ethnicity, socioeconomic status) to monitor our inclusivity.

Contact with General Practitioner

Patient GPs will be informed of the participant's enrolment in the study as part of the usual NHS discharge procedure at site. The study will not mandate that the site teams are required to send a separate, additional letter to the participant's GP.

Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

End of Study Definition

This clinical study will end when the specified number of participants have been recruited, and all participants have completed their 12-month follow-up, and the database is hard locked.

Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10 DATA MANAGEMENT

Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data. What constitutes the source data for this trial will be outlined in the Source Data agreement.

Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

Database

Trial data will be collected on an electronic case report form (eCRF). Data will be entered via web-based database through electronic data capture (EDC). The database used to capture this information is the OpenClinica database. Data is entered into the database by the site team. The database will raise automatic queries and allow manual queries to also be raised which will be checked and validated by the Trial Manager and Monitor. All data, changes to data and query resolution will be included in an audit trail including dates. Specific instructions on how to enter data and deal with queries are detailed in the eCRF completion guide. Automated Randomisation will be carried out using the OpenClinica system in accordance with ICTU specific SOPs.

Serious Adverse Events (SAEs) will be captured in the eCRF and will require sign off by the Principal Investigator at the site.

Data Collection

All data for the study will be entered into the eCRF via the OpenClinica database. These data will include demographics, previous medical history, blood results, vital signs, organ support and follow-up information. Details of procedures for eCRF completion will be provided in a study manual.

Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11 STUDY MANAGEMENT STRUCTURE

The day-to-day management of the trial will be co-ordinated through the Imperial Clinical Trials Unit and the Chief Investigator. The following groups and trial committees will be established:

Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager and at least one lay member. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter. A copy of all TSC meeting minutes will be sent to RGIT.

Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be convened including as a minimum an independent Chair, independent clinician, and independent statistician. It will include suitable experienced clinicians / clinical trialists and statisticians. The role of the DMC is advisory to the TSC and Sponsor and will provide overall supervision of trial safety. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter. It is the only committee that will review aggregated unblinded data.

Early Discontinuation of the Study

The internal pilot study as detailed above will be used as a way to determine feasibility of the trial. If the findings of the pilot study determine it is not feasible then stopping the trial will be considered. The DMC may recommend early stopping of the trial or any intervention if there is a safety issue. If these instances arise, guidance will be provided to local sites about continuation of interventions and follow-up visits.

Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. Risk assessment will be carried out by the ICTU Head of QA in collaboration with the Chief Investigator and Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

Monitoring

The study will be monitored periodically by a trial monitor to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

A monitoring plan will be devised based on risk analysis and described in detail in the monitoring manual by the project manager. Initiation visits will be conducted for all sites prior to the recruitment of participants. These visits will be conducted either remotely or on site depending on availability of the site and study team.

The trial will involve a combination of central, remote and on-site monitoring. On site visits will be conducted by trained monitors during the recruitment phase of the trial and after the trial as required by the protocol and trial procedures according to the monitoring manual to ensure participant safety, accurate data collection and reporting. Central monitoring will be conducted regularly where data queries and protocol deviations are reviewed, and any required further site training is conducted.

Remote monitoring will also be utilised with sites in between on-site visits, to enable the study team to complete knowledge checks and follow up with training for new site members.

Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

Peer review

This trial was externally peer reviewed as part of the NIHR EME funding process.

Patient and Public Involvement

Patient and Public Involvement (PPI) has been integral to the development of this proposal. The initial choice of interventions was based on the ECMONet research prioritisation exercise. We sought feedback on the trial design, interventions, outcome measures, consent process from patients and relatives through patient and family advisory group including ICU/ECMO survivors. There are two PPI co-applicants on the NIHR EME award funding the study and they are also part of the Trial Management Group.

A lay representative will sit on the Trial Steering Committee and will provide input from a patient perspective at trial meetings. The representative will provide valuable insight in trial management, study procedures, as well as any amendments we make to the study in the future. They will also contribute to result interpretation, reporting and dissemination.

Publication and Dissemination policy

We will publish the main results in major international peer-reviewed journals. We will ensure all publications meet UKRI open access policies. These publications will be in addition to the final NIHR EME report. We will set up a trial website that will provide information about the trial, including the easy read style and animated clip to provide patients and relatives with information about the trial. We will provide regular updates about the trial on the website and across the national and international ECMO network. Final results will be publicly available on this website and all findings will be disseminated to participants.

It is understood by the investigator that the Sponsor will use information developed in this clinical study testing the near-apnoeic ventilation strategy during ECMO support and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results, and all data developed during this study to the Sponsor. Information concerning the study, patent applications, processes, scientific data or other pertinent information remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Permission from the Executive/Writing Committee is necessary prior to disclosing any information relative to this study outside of the Trial Steering Committee. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the investigator(s), but the Sponsor will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

12 REFERENCES

1. Hodgson CL, Fulcher B, Mariajoseph FP, Burrell AJC, Pellegrino V, Brodie D, et al. A Core Outcome Set for Research in Patients on Extracorporeal Membrane Oxygenation. Crit Care Med. 2021;49(12):e1252–4.

2. Blackwood B, Ringrow S, Clarke M, Marshall JC, Connolly B, Rose L, et al. A Core Outcome Set for Critical Care Ventilation Trials. Crit Care Med. 2019;47(10):1324–31.

3. Gorman EA, O'Kane CM, McAuley DF. Acute respiratory distress syndrome in adults: diagnosis, outcomes, long-term sequelae, and management. Lancet. 2022;400(10358):1157–70.

4. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. Jama. 2016;315(8):788–800.

5. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and Outcomes of Acute Lung Injury. N Engl J Med. 2005;353(16):1685–93.

6. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med. 2011;364(14):1293–304.

7. Slutsky AS, Ranieri VM. Ventilator-Induced Lung Injury. N Engl J Med. 2013;369(22):2126–36.

8. Munshi L, Brodie D, Fan E. Extracorporeal Support for Acute Respiratory Distress Syndrome in Adults. NEJM Évid. 2022;1(10).

9. Network ARDS, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. N Engl J Med. 2000;342(18):1301–8.

10. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2013;368(23):2159–68.

11. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, et al. Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome. Am J Resp Crit Care. 2007;175(2):160–6.

12. Hager DN, Krishnan JA, Hayden DL, Brower RG, Network ACT. Tidal Volume Reduction in Patients with Acute Lung Injury When Plateau Pressures Are Not High. Am J Resp Crit Care. 2005;172(10):1241–5.

13. Zochios V, Brodie D, Shekar K, Schultz MJ, Parhar KKS. Invasive mechanical ventilation in patients with acute respiratory distress syndrome receiving extracorporeal support: a narrative review of strategies to mitigate lung injury. Anaesthesia. 2022;77(10):1137–51.

14. Abrams D, Schmidt M, Pham T, Beitler JR, Fan E, Goligher EC, et al. Mechanical Ventilation for Acute Respiratory Distress Syndrome during Extracorporeal Life Support. Research and Practice. Am J Resp Crit Care. 2019;201(5):514–25.

15. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensiv Care Med. 2016;42(10):1567–75.

16. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, et al. Mechanical Power and Development of Ventilator-induced Lung Injury. Anesthesiology. 2016;124(5):1100–8.

17. Urner M, Jüni P, Hansen B, Wettstein MS, Ferguson ND, Fan E. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. Lancet Respir Med. 2020;8(9):905–13.

18. Gattinoni L, Tonetti T, Quintel M. How best to set the ventilator on extracorporeal membrane lung oxygenation. Curr Opin Crit Care. 2017;23(1):66–72.

19. Graf PT, Boesing C, Brumm I, Biehler J, Müller KW, Thiel M, et al. Ultraprotective versus apneic ventilation in acute respiratory distress syndrome patients with extracorporeal membrane oxygenation: a physiological study. J Intensive Care. 2021;10(1):12.

20. Sorbo LD, Goffi A, Tomlinson G, Pettenuzzo T, Facchin F, Vendramin A, et al. Effect of Driving Pressure Change During Extracorporeal Membrane Oxygenation in Adults With Acute Respiratory Distress Syndrome: A Randomized Crossover Physiologic Study. Crit Care Med. 2020;48(12):1771–8.

21. Lyons C, Callaghan M. Uses and mechanisms of apnoeic oxygenation: a narrative review. Anaesthesia. 2019;74(4):497–507.

22. Lohser J, Slinger P. Lung Injury After One-Lung Ventilation: A Review of the Pathophysiologic Mechanisms Affecting the Ventilated and Collapsed Lung. Surv Anesthesiol. 2016;60(3):98–9.

23. Mauri T, Eronia N, Abbruzzese C, Marcolin R, Coppadoro A, Spadaro S, et al. Effects of Sigh on Regional Lung Strain and Ventilation Heterogeneity in Acute Respiratory Failure Patients Undergoing Assisted Mechanical Ventilation*. Crit Care Med. 2015;43(9):1823–31.

24. Mauri T, Foti G, Fornari C, Grasselli G, Pinciroli R, Lovisari F, et al. Sigh in Patients With Acute Hypoxemic Respiratory Failure and ARDS The PROTECTION Pilot Randomized Clinical Trial. Chest. 2021;159(4):1426–36.

25. Pesenti A, Carlesso E, Langer T, Mauri T. Ventilation during extracorporeal support. Medizinische Klinik - Intensivmedizin Und Notfallmedizin. 2018;113(Suppl 1):26–30.

26. Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, et al. Near-Apneic Ventilation Decreases Lung Injury and Fibroproliferation in an Acute Respiratory Distress Syndrome Model with Extracorporeal Membrane Oxygenation. Am J Resp Crit Care. 2018;199(5):603–12.

27. Schmidt M, Pham T, Arcadipane A, Agerstrand C, Ohshimo S, Pellegrino V, et al. Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. An International Multicenter Prospective Cohort. Am J Resp Crit Care. 2019;200(8):1002–12.

28. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. New Engl J Med. 2018;378(21):1965–75.

29. Warren A, Chiu YD, Villar SS, Fowles J anne, Symes N, Barker J, et al. Outcomes of the NHS England National Extracorporeal Membrane Oxygenation Service for adults with respiratory failure: a multicentre observational cohort study. Brit J Anaesth. 2020;125(3):259–66.

30. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, et al. Position Paper for the Organization of Extracorporeal Membrane Oxygenation Programs for Acute Respiratory Failure in Adult Patients. Am J Resp Crit Care. 2014;190(5):488–96.

31. Combes A, Bacchetta M, Brodie D, Müller T, Pellegrino V. Extracorporeal membrane oxygenation for respiratory failure in adults. Curr Opin Crit Care. 2012;18(1):99–104.

32. FORCE TADT. Acute Respiratory Distress Syndrome: The Berlin Definition. Jama. 2012;307(23):2526–33.

33. SCHULMAN S, KEARON C, HAEMOSTASIS the SOCOAOTSASCOTISOTA. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692–4.

34. Dimairo M, Pallmann P, Wason J, Todd S, Jaki T, Julious SA, et al. The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design. BMJ. 2020;369:m115.

35. Aalen, O. O. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. Scandinavian Journal of Statistics. 1978;5(3):141–50.

36. Allignol A, Schumacher M, Wanner C, Drechsler C, Beyersmann J. Understanding competing risks: a simulation point of view. BMC Méd Res Methodol. 2011;11(1):86.

37. Geskus RB. Competing Risks: Concepts, Methods, and Software. Annu Rev Stat Appl. 2023;11(1):227–54.

38. Baayen C, Volteau C, Flamant C, Blanche P. Sequential trials in the context of competing risks: Concepts and case study, with R and SAS code. Stat Med. 2019;38(19):3682–702.

13 REVISION HISTORY

Version	Date	Summary of changes
1.0	19 SEPT 2025	First version

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Rest Or Moderate mechanical ventilation during ECMO Support

Protocol Number: 175660

Signed: _____

Dr Brijesh Patel
Clinical Senior Lecturer in Cardiothoracic Critical Care

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Rest Or Moderate mechanical ventilation during ECMO support

Protocol Number: 175660

Signed: _____

Dr Ruth Nicholson
Head of Research Governance and Integrity
Imperial College, London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: **Rest Or Moderate mechanical ventilation during ECMO support**

Protocol Number: 175660

Signed: _____

Dr Leila Janani
Senior Statistician
Imperial College, London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: **Rest Or Moderate mechanical ventilation during ECMO support**

Protocol Number: 175660

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES

Appendix 1: Visit Schedule

	Pre-ECMO	At Randomisation (Day 0)	Daily data**	Discharge to 60 Days (+/- 7 days)	Discharge to 6 months (+/- 2 months)	1 year (+/- 2 months)
Consent		X				
Inclusion/Exclusion criteria		X				
Demographic data		X				
Date/time of consent and randomisation		X				
Date and time of Hospital and ICU admission		X				
Assessment of functional status including co-morbidities (inc concomitant medication)		X				
Social history		X				
Cause of ARDS	X					
Date/time initiation of invasive mechanical ventilation	X					
Prior use of adjunctive ARDS therapies including NMBD, prone position, recruitment maneuvers	X		X			
Date/time initiation of ECMO		X				
Type of ECMO configuration		X				
Mechanical Ventilation parameters **especially set and actual respiratory rate**	X	X	X			
Clinical rationale for cessation of NAV			X			
ECMO parameters		X	X			
Date/time of ECMO sweep off			X			
Date/time of ECMO explantation/decannulation			X			
Arterial blood gas	X	X	X			
Fluid balance – cumulative and daily	X	X	X			
Vasopressor / Inotropic agent usage	X	X	X			
Diuretic usage and use of renal replacement therapy	X	X	X			
Laboratory results in last 24 hours	X	X	X			

Microbiological results to date	X	X	X			
ICU and pre-/post-ICU hospital CT, echocardiography, and CXR imaging			X (when clinically indicated and performed)	X (when clinically indicated and performed)	X (when clinically indicated and performed)	X (when clinically indicated and performed)
Serious adverse events to hospital discharge (including AEs of specific interest related to ECMO)			X	X	X	X
Days alive and free of ECMO (DAFE) up to day 28 and 60			X	X		
Daily Organ Support for participants on ECMO (DOSE) score up to 28 days post-randomization			X	X		
Mortality at 60 days, 6 months, and 1 year				X	X	X
First successful liberation from invasive mechanical ventilation			X	X	X	X
Duration of invasive mechanical ventilation			X	X	X	X
Length of total ICU and hospital stay			X	X	X	X
Health-related quality of life (EQ-5D-5L) at 6 and 12 months					X	X
Disability (Modified Rankin Scale) at 6 and 12 months					X	X
Date and time of death			X	X	X	X

For physiological and biological sampling please refer to separate schedule of events.

APPENDIX 2: MECHANISTIC ANALYSES

The pathobiological, pathophysiological, and radiological processes involved in the progression and resolution of ARDS and VILI are poorly understood. The ROMEO study offers a unique opportunity to longitudinally assess and characterise the impact to near-apnoeic ventilation strategy on the clinical, physiological, and biological progression and resolution of ARDS supported on ECMO.

1. ROMEO Biology - Biological Sampling

The sampling will depend on which TIER a particular site comes under. Samples should be collected in accordance with informed consent rules and legislation described elsewhere in the ROMEO Trial protocol. The date of randomisation may differ from the date of ICU admission. Here, all samples are described related to the date and time of randomization in the ROMEO Trial.

To minimize participant discomfort, blood should be collected from existing central lines or arterial lines, where possible. No lines should be placed as part of this study for blood collection. For participants who do not have any vascular access, blood collection should be done by venepuncture. It is important that the blood is NOT haemolysed for the analysis to be valid. If the sample is haemolysed, another tube of blood may be drawn. If repeat sampling is not possible, then the haemolysed sample can be processed with a note written in the Specimen Collection Form to indicate that the sample is haemolysed.

- **Blood sampling** at pre-ECMO* (T0); on arrival to ECMO unit (T1) (i.e. at randomisation), and a sample between days 3-5 (T2 (preferably on same day as BAL)), and weekly (T3+, etc) thereafter when in ICU until decannulation from ECMO.

  *Given the urgent nature of ECMO, a sample of blood will be taken prior to starting ECMO (T0) and hence, often prior to discussion with personal nominee (**For sites in Scotland** Welfare Guardian), at the discretion of the clinical team. This has been undertaken on previous ECMO studies performed at GSTT with patient and public and REC support. If the participant is not enrolled into the study, then this sample will be discarded.

- **Bronchoscopic sampling**, (performed at some study sites) with bronchoalveolar lavage (BAL) and deep bronchial brushes (where possible), will be sampled at baseline ($T1_{BAL}$) and between days 3-5 ($T2_{BAL}$). If the patient undergoes a bronchoscopy for clinical purposes, samples will be taken for research purposes dependent on the time of sampling ($T3+_{BAL}$). Bronchial brushing maybe performed in some patients.

Excess blood and bronchoscopy samples taken by the clinical team for clinical purposes at the same time-points above may be stored and processed in a similar manner and be utilised for research purposes to reduce sampling at any time-points above.
The day of sampling may fall on weekends / holidays when staff are not available. If this does occur, samples/scans will be taken/performed on the day prior/next available day. This will be recorded on the CRF and also on the sample accountability log, along with the day the samples were taken (e.g. day 8 instead of day 7). Blood sampling will be collected by trained study staff and processed according to standardised procedures.
Additional blood samples (40ml) may be taken at various time-points for leukocyte isolation. Given the uncertain nature of time of insult, Bronchoscopy and BAL will be undertaken where possible and

processed. Participants will be closely monitored during and after bronchoscopy and BAL. A sample will be sent for microbiological analysis.

Research samples will be taken at set time points as summarised below:

Longitudinal Blood Sampling	Blood tubes required				
	EDTA	Citrate	SST	Li-Hep	PAX Gene (RNA)
Blood volume per tube (mls):	10	8	9	9	2.5
T0 Pre-ECMO	X	X	X	X	X
T1 On ECMO unit - at randomisation	X	X	X	X	X
T2 Between Day 3 & 5 post randomisation	X	X	X	X	X
T3+ Day 7 Post randomisation then weekly and at decannulation from ECMO	X	X	X	X	X

Bronchoscopy sampling

$T1_{BAL}$ On ECMO unit at randomisation	X
$T2_{BAL}$ Between Day 3 & 5 post randomisation	X
$T3+_{BAL}$ When clinically indicated	X

Discontinuation of sampling. A study participant may revoke their consent to provide samples for the trial, even if their participation in the trial is continued. This withdrawal of consent for specimen collection will be reflected in the patient information forms. Participants (or their legally authorized representatives) may request to have already collected samples destroyed. These requests will be logged in the ROMEO Trial CRF.

2. ROMEO Physiology

Data collected will depend on which TIER a site comes under. Basic physiological measurements will be collected by all sites as part of the ROMEO CRF.

TIER 2. Additionally, more complex physiology will be performed.
One or more of the measurements below to be acquired pre-randomisation and within 48 hours of randomisation.

- At enrolment, measurement of the recruitment to inflation ratio
- At enrolment and within 48 hours of randomisation a 0-40cmH2O low flow (<10L) inspiratory and expiratory pressure volume loop will be acquired to obtain the following:
    - Inspiratory capacity (mls)
    - Airway opening pressure on a 0-40cmH2O low flow (<10L) pressure volume loop
    - Maximal hysteresis (volume difference) between the inspiratory and expiratory limbs
- Daily recording of the volume of expired CO2 per minute from volumetric capnography (if available), concurrent with the TIER 1 physiological measurements
- Echocardiogram

TIER 3 Balloon Physiology

- Oesophageal pressure at end inspiration and and expiration, obtained concurrently with the TIER 1 physiology measurements
- Central venous or pulmonary arterial pH, PaO2, PaCO2, HCO3, Base Excess, Lactate, Haemoglobin as measured at 37°C

- Pre- and Post-membrane oxygenator pH, PaO2, PaCO2, HCO3, Base Excess, Lactate, Haemoglobin as measured at 37°C
- Pulmonary arterial systolic, diastolic and mean pressures
- Cardiac output (from echocardiography or pulmonary artery catheterisation)
- Electrical Impedance Tomography data (where available)

Biological and Physiological sampling tiers

Sites will be allocated to a sampling tier in accordance with the resources available at each site. Table below shows requirements for each TIER.

	TIER 1	TIER 2a	TIER 2b	TIER 3
Blood	All blood tubes	All blood tubes	All blood tubes	All blood tubes
Bronchoscopy		BAL	BAL	BAL & Brush
Physiology			Complex	Complex & Balloon

3. ROMEO Radiology

All patients routinely receive Chest imaging (chest x-ray and CT scans) as well as transthoracic / oesophageal echocardiography as part of usual care on admission to ICU. We will collect these routine imaging data to inform physiological and biological analyses.

Baseline CT scan data

All patients are routinely CT scanned as part of usual care on admission to ICU once ECMO catheters have been sited but prior to initiation of ECMO. We will collect this baseline CT imaging data which includes

1. CT chest to assess 'recruitability' with continuous positive airway pressure (CPAP) of 5 cmH_2O and then repeated with CPAP of 45 cmH_2O – unless contraindicated (e.g., severe haemodynamic instability of untreated air leaks).
2. non-contrast CT head is performed to assess for intracranial haemorrhage
3. post contrast portal venous phase imaging of the abdomen to assess catheter placement and acute abdominal pathology