The REST Study

pRotective vEntilation with veno-venouS lung assisT in respiratory failure

A pragmatic randomised controlled trial to determine whether Veno-Venous Extracorporeal Carbon Dioxide Removal (VV-ECCO$_2$R) in mechanically ventilated patients with hypoxaemic respiratory failure improves 90 day mortality

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PROTOCOL AUTHORISATION

Protocol Title:	p**R**otective v**E**ntilation with veno-venou**S** lung assis**T** in respiratory failure
Protocol Acronym (if applicable):	The **REST** Trial
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A review of the protocol has been completed and is understood and approved by the following:

Danny McAuley		DD / MM / YYYY
Chief Investigator	Signature	Date
James McNamee		DD / MM / YYYY
Clinical Lead	Signature	Date
Cliona McDowell		DD / MM / YYYY
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
ABG	Arterial Blood Gas
ADE	Adverse Device Effect
AD8	AD8 Dementia Screening Interview
AE	Adverse Event
APRV	Airway Pressure Release Ventilation
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
BAL	Bronchoalveolar lavage
BHSCT	Belfast Health and Social Care Trust
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
CL	Clinical Lead
CMP	Case Mix Programme
CO_2	Carbon Dioxide
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQoL-5 Dimension Questionnaire (5 level version)
$ECCO_2R$	Extracorporeal Carbon Dioxide Removal
ECMO	Extracorporeal Membrane Oxygenation
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HFOV	High Frequency Oscillatory Ventilation
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICS	Intensive Care Society
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicines and Healthcare products Regulatory Agency
MoCA-BLIND	Montreal Cognitive Assessment/MoCA-Blind
NHS	National Health Service
NICTU	Northern Ireland Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMBD	Neuromuscular Blocking Drugs
$PaCO_2$	Partial Pressure of Carbon Dioxide in arterial blood
PaO_2	Partial Pressure of Oxygen in arterial blood
PBW	Predicted Body Weight
PEEP	Positive End Expiratory Pressure
P/F ratio	PaO_2/FiO_2 ratio
PI	Principal Investigator
Pplat	Plateau Pressure
PTSD	Post Traumatic Stress Disorder
PTSS 14	Post Traumatic Stress Syndrome Questionnaire

QALY	Quality Adjusted Life Year
QUB	Queens University Belfast
REC	Research Ethics Committee
RMP	Registered Medical Practitioner
RR	Respiratory Rate
SADE	Severe Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SICSAG	Scottish Intensive Care Society Audit Group
SOFA	Sequential Organ Failure Assessment
SOPs	Standard Operating Procedures
SGRQ	St George's Respiratory Questionnaire
TAPSE	Tricuspid Annular Plane Systolic Excursion
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Suspected Serious Adverse Device Effect
VAS	Visual Analogue Scale
VILI	Ventilator Induced Lung Injury
VV-ECCO$_2$R	Veno-Venous Extracorporeal Carbon Dioxide Removal
Vt	Tidal Volume

1 STUDY SUMMARY

Scientific title	p**R**otective v**E**ntilation with veno-venou**S** lung assis**T** in respiratory failure Acronym: The REST Trial
Public title	A trial of a new way of treating patients with respiratory failure
Health condition studied	Acute hypoxaemic respiratory failure
Study Design	Randomised, allocation concealed, controlled, open, pragmatic clinical and cost effectiveness trial
Study Aim and Objectives	The primary objective is to determine whether VV-$ECCO_2R$ and lower tidal volume mechanical ventilation in patients with acute hypoxaemic respiratory failure decreases mortality 90 days after randomisation. Secondary objectives are to determine the effects of VV-$ECCO_2R$ on: 1) Tidal volumes 2) Duration of mechanical ventilation 3) Requirement for ECMO 4) Long-term mortality 5) Health Related Quality of Life 6) Safety 7) Cost-effectiveness in the NHS setting 8) Long term respiratory morbidity
Study Intervention	VV-$ECCO_2R$ and lower tidal volume mechanical ventilation (target tidal volume of ≤ 3ml/kg predicted body weight and a Pplat ≤ 25cmH_20)
Primary Outcome	Mortality at 90 days after randomisation
Key Secondary Outcomes	1) Tidal volumes 2) Ventilator free days at 28 days 3) ECMO use up to 7 days 4) Mortality at 28 days, 6 months and 1 year 5) HRQoL at 6 months and 1 year 6) Adverse event rate 7) Health & Social Care Service costs at 6 months and 1 year 8) Long term respiratory morbidity and requirement for home oxygen
Study Setting	At least 40 adult intensive care units
Target Sample Size	1120 participants (560 in each arm)
Study Duration	65 months

2 STUDY TEAM

Chief Investigator	**Professor Danny McAuley** Queens University Belfast
Clinical Lead	**Dr James McNamee** Belfast Health & Social Care Trust
Co-Investigators	**Dr Nicholas Barrett** Guys and St Thomas' NHS Foundation Trust
	Professor Richard Beale Kings College London and Guys and St Thomas' NHS Foundation Trust
	Dr Andrew Bentley University Hospital of South Manchester NHS Foundation Trust
	Dr Andrew Bodenham Leeds Teaching Hospital NHS Trust
	Dr Stephen Brett Imperial College Healthcare NHS Trust
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	Dr Anthony Gordon Charing Cross Hospital and Imperial College London
	Dr Mark Griffiths Royal Brompton and Harefield NHS Foundation Trust
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	Professor Tim Walsh University of Edinburgh, Scotland
	Dr Matthew Wise Cardiff and Vale University Local Health Board, Wales
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Primary Sponsor's Reference	15084DMcA-AS
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3 FUNDING

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme will be providing the research costs to the REST study (Reference 13/141/02).

The study is funded as a result of a commissioned call from the NIHR HTA.

Additional costs associated with the $ECCO_2R$ equipment along with the required training will be supported by the $ECCO_2R$ device manufacturer.

4 ROLES AND RESPONSIBILITIES

4.1 Sponsor

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation undertaking Sponsor-delegated duties in relation to the management of the study.

4.2 Committees

4.2.1 Trial Management Group (TMG)

A TMG will be established and chaired by the CI or delegated to the Clinical Lead (CL). It will have representatives from the Clinical Trials Unit (CTU) and co-investigators, and will meet face to face or by teleconference on a monthly basis and will communicate between times via telephone and email as needed. The roles and responsibilities of the TMG will be detailed in the Trial Management Group Charter. Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All the day-to-day activity will be managed by the Trial Manager/Co-ordinators.

4.2.2 Trial Steering Committee (TSC)

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

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

4.2.3 Data Monitoring and Ethics Committee (DMEC)

The independent DMEC will be comprised of at least 2 independent clinicians with experience in clinical trials, and an independent statistician. One of the independent clinicians will have experience in the regulatory aspects of clinical trials involving medical devices.
The role of the independent DMEC will be detailed in the DMEC charter but will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies. The independent DMEC will meet at least 6 monthly and additional meetings can be convened if the event of any safety concerns.

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

4.2.4 User Involvement or any other relevant committees

The study will be registered with the INVOLVE open-access database which registers research health care projects involving members of the public as partners in the research process (http://www.invo.org.uk). Patient experience whilst critically ill will be taken into consideration when preparing patient information leaflets and consent forms. Barry Williams (previous Chairman of the Critical Care patient group CritPal; now known as PatRel) will represent the patient's perspective on the TSC ensuring that the trial remains considerate of the needs of the patients and their families.

5 BACKGROUND AND RATIONALE

5.1 Background Information

Acute hypoxaemic respiratory failure requiring mechanical ventilation is a major cause of morbidity and mortality. A significant proportion of affected patients will have the Acute Respiratory Distress Syndrome (ARDS). ARDS is characterised by non-cardiogenic pulmonary oedema (identified by bilateral infiltrates on chest X-ray) alongside a requirement for supplementary oxygen to maintain normal arterial oxygen tension. Acute hypoxaemic respiratory failure and ARDS occur in response to a variety of insults, such as trauma, pneumonia and severe sepsis; affect all age groups; have a high mortality of up to 30-50% and cause a long-term reduction in quality of life for survivors (1, 2). Acute hypoxaemic respiratory failure has significant resource implications in terms of ICU and hospital stay (3). The cost per ICU bed-day exceeds £1800 and delivery of critical care to patients with acute hypoxaemic respiratory failure accounts for a significant proportion of ICU capacity. In addition, survivors often have long-term physical and cognitive impairment requiring support in the community and many survivors are unable to return to work 12 months after hospital discharge. The high incidence, mortality, long-term consequences and high economic costs mean that acute hypoxaemic respiratory failure is an extremely important problem.

In the UK over 100,000 patients each year require mechanical ventilation, of whom over 15,000 patients have acute hypoxaemic respiratory failure as defined in our planned study population (unpublished data UK Intensive Care National Audit & Research Centre). Over the past few decades significant progress has been made in understanding the pathophysiology of acute hypoxaemic respiratory failure and ARDS (4). Mechanical ventilation is often required to provide adequate gas exchange and although it is life-saving in this setting, it is also now known to contribute to the morbidity and mortality in the condition. Ventilators delivering high pressures and volumes cause regional over distension in the injured lung resulting in further inflammation and non-cardiogenic pulmonary oedema. The release of inflammatory mediators from the damaged lung causes systemic inflammation leading to multi-organ failure and death (5).

5.2 Rationale for the Study

The few interventions that have been shown to reduce the high mortality in these patients have targeted ventilator-induced lung injury (VILI) (6-10). A landmark trial by the ARDSNet trials group found that ventilating patients with acute hypoxaemic respiratory failure secondary to ARDS with a lung protective strategy aiming for a reduced tidal volume of 6ml/kg PBW and a maximum end-inspiratory Pplat ≤ 30cmH_2O decreased mortality from 40% (in the conventional arm treated with tidal volume less than 12ml/kg PBW) to 31% (6). Furthermore in a cohort of 485 patients with hypoxaemic respiratory failure secondary to ARDS, long-term mortality at 2-years was improved in patients compliant with lung protective ventilation during their ICU stay (11). It is accepted that implementing protective lung ventilation saves lives (estimated 2 patients' lives/day in the UK extrapolating ARDSNet data to the UK) and is cost effective. Extrapolating US data to the UK, in terms of Quality Adjusted Life Years (QALYs) gained, if an average ICU spent £6000 per patient with ARDS on an intervention in order to achieve more than 90% adherence to low tidal volume ventilation the intervention would still be cost effective (12).

Recent studies have shown that lung hyperinflation and injury still occur in approximately 30% of ARDS patients even though they are being ventilated using the ARDSNet strategy (13). Additionally, using more protective ventilation compared to conventional protective ventilation was associated with further reduction in mortality as the Pplat decreases below 28cmH_2O (14). This analysis also suggested a beneficial effect of further tidal volume reduction even for patients who already had a Pplat ≤ 30cmH_2O. However tidal volume reduction to < 6ml/kg

PBW can be associated with secondary systemic effects associated with raised blood carbon dioxide levels, such as elevated intracranial pressure, pulmonary hypertension, altered myocardial contractility and decreased renal blood flow. Therefore more protective mechanical ventilation strategies are difficult to achieve for most patients on conventional mechanical ventilation for moderate to severe respiratory failure.

5.3 Veno-venous Extracorporeal Carbon Dioxide Removal (VV-ECCO$_2$R)

Extracorporeal carbon dioxide removal (ECCO$_2$R) in association with mechanical ventilation offers a potentially attractive solution to permit tidal volume reduction to less than 6ml/kg PBW and to achieve low plateau pressures (< 25cmH$_2$O). Using these extracorporeal circuits, carbon dioxide can be 'dialysed' out of the blood while the lungs are ventilated in a more protective manner (15). Techniques to achieve ECCO$_2$R have existed since the late 1970s but widespread uptake has been limited due to the paucity of trial data, the demanding technical requirements with the devices originally used, and concerns regarding complications, particularly associated with arterial cannulation where arterio-venous ECCO$_2$R devices were used. In an observational study conducted in the 1980's, the use of VV-ECCO$_2$R in addition to low frequency mechanical ventilation resulted in lower than expected mortality in a cohort of patients with severe ARDS (16). However, a randomised, controlled single-centre study using that same technology in the 1990s was stopped early for futility after only 40 patients had been recruited and failed to demonstrate a survival benefit with this device (17). These early inefficient devices required high extracorporeal blood flows and large intravascular cannulae and they were associated with significant complications, hence their use was restricted to specialist cardiothoracic centres. In addition the devices did not use biocompatible materials and therefore the high level of systemic anticoagulation necessary to prevent clotting in the extracorporeal circuit was associated with significant haemorrhagic complications.

In recent years, more efficient veno-venous (VV-ECCO$_2$R) devices have become available. These have replaced arterio-venous devices and have the advantage of not requiring arterial puncture. These can achieve carbon dioxide removal with relatively low extracorporeal blood flows (0.4−1 l/min) requiring only a smaller dual lumen venous catheter. In addition these ECCO$_2$R devices use more biocompatible materials making the device more resistant to clot formation and cause less platelet and clotting factor consumption. Therefore only minimal systemic anticoagulation is required which reduces the likelihood of bleeding complications (15). These devices are now comparable to renal dialysis equipment, which is routinely used safely as standard care in ICUs in the UK. Recent registry data released on the use of VV-ECCO$_2$R in 129 patients demonstrated a risk and safety profile similar to continuous renal replacement therapy (CRRT) devices facilitating significant reductions in mechanical ventilation plateau pressures (2015 Hemolung Registry Report).

5.4 Clinical Trials of ECCO$_2$R to date

We have recently completed a systematic review to assess feasibility, complication rates and efficacy of extracorporeal CO_2 removal devices in acute respiratory failure and ARDS. We included randomised controlled trials and observational studies. The review included 14 studies with 495 patients (2 randomised controlled trials and 12 observational studies). Given the variation in study design, a meta-analysis was considered to be inappropriate and data were descriptively synthesised. Overall there was a paucity of high quality data (18).
Arterio-venous ECCO$_2$R was used in seven studies, and veno-venous devices in seven. Carbon dioxide removal was shown to be feasible, facilitating the use of lower, more protective tidal volume ventilation. Studies conducted before the year 2000 reported higher rates of haemorrhagic complications, with the reduction in more recent studies likely representing technological advances. There was no survival benefit with ECCO$_2$R, although a post hoc analysis of data from the most recent randomised controlled trial showed an improvement in ventilator free days in patients with more severe hypoxia as defined by a PaO_2/FiO_2 ratio ≤ 20kPa (19). In addition although the optimal timing of the use of ECCO$_2$R remains unclear,

early usage may be more beneficial. While there was a trend towards improved outcomes as indicated by more ventilator free days with the application of modern $ECCO_2R$ in patients with more severe respiratory failure definitive data are, as yet, lacking. Our review indicates a state of clinical equipoise on the benefits of $ECCO_2R$ in acute respiratory failure (18).

A 2010 Canadian Health Technology Assessment review found that $ECCO_2R$ was efficacious for CO_2 removal and could therefore potentially facilitate lung protective ventilator strategies, but like our review, found no evidence of improved long-term survival (20). The UK NICE guidelines on $ECCO_2R$ state that evidence on its efficacy is limited in quantity and quality and calls for more clinical trials on these devices (21).

Currently there are a number of trials evaluating the use of $ECCO_2R$ in intensive care patients. NCT02260583, NCT02107222 and NCT02086084 will evaluate $ECCO_2R$ use in hypercapnic respiratory failure secondary to COPD exacerbations. This indication has been summarised in a recent systematic review and concluded that although it is still experimental it appears to have a benefit in COPD exacerbations but higher-quality studies are required to better elucidate this risk-benefit balance (22).

With regard to its use in hypoxaemic respiratory failure a European study SUPERNOVA (Strategy of UltraProtective Lung Ventilation With Extracorporeal CO_2 Removal for New-Onset Moderate to seVere ARDS) NCT02282657 is in pilot phase and aims to recruit patients with ARDS as does a trial in Singapore, U-Protect (Ultra-protective Pulmonary Ventilation Supported by Low Flow $ECCO_2R$ for Severe ARDS) NCT02252094 and a further trial in Belgium NCT01911533. A recently published series of 9 patients using VV-$ECCO_2R$ and lower tidal volume ventilation demonstrated that this technique is safe providing adequate gas exchange (23).

5.5 Current use of $ECCO_2R$ in the UK

As the technology to deliver VV-$ECCO_2R$ has become simpler, it is increasingly being adopted into clinical practice. Two recent surveys have demonstrated increasing usage of this technology despite the lack of evidence. We have undertaken a national survey endorsed by the UK Intensive Care Society. Of 321 responses, 36% of respondents would use $ECCO_2R$ to treat a patient with severe respiratory failure receiving protective ventilation. In addition 92% would consider taking part in a clinical trial to determine its effectiveness (presented at UK ICS conference 2011). A NICE commissioned $ECCO_2R$ Evaluation Steering Group based at the Universities of Birmingham and Brunel also carried out an independent survey on national use of $ECCO_2R$ in the UK. Of 141 responses from ICU clinical leads, 33% of respondents had already used $ECCO_2R$ and 75% said they would consider using it in the future (Personal communication; A Chapman). These data demonstrate that many sites are already using these devices on an ad-hoc basis. Wide dissemination of $ECCO_2R$ technology at this time in the absence of high quality evidence would represent premature adoption of a technology without rigorous evaluation of associated risks and benefits. Specifically, potential benefits must be balanced against risks associated with catheter insertion and extracorporeal blood circulation.

Together this highlights the need for a large randomised controlled trial to establish whether VV-$ECCO_2R$ in acute hypoxaemic respiratory failure can allow the use of a more protective ventilatory strategy and is associated with improved patient outcomes. Importantly, if there was no benefit, the trial would provide evidence to stop the widespread adoption of an expensive and ineffective or potentially harmful treatment in this setting.

5.6 Why do a study now?

The use of extracorporeal carbon dioxide removal in acute respiratory failure is important to the UK intensive care community. The need for a randomised controlled trial in this area was proposed at the UK Intensive Care Society research prioritisation exercise in 2010 and was ranked highly. Subsequently the NIHR Health Technology Assessment board issued a commissioned call brief for a clinical trial to determine the clinical and cost effectiveness of VV-ECCO$_2$R in patients with hypoxaemic respiratory failure.

6 STUDY AIM AND OBJECTIVES

6.1 Research Hypothesis

In adult patients who require invasive mechanical ventilation for acute hypoxaemic respiratory failure, VV-ECCO$_2$R and lower tidal volume ventilation results in reduced mortality.

6.2 Study Aim

We propose to deliver a multi-centre clinical trial to determine whether VV-ECCO$_2$R and lower tidal volume mechanical ventilation improves outcomes and is cost-effective, in comparison with standard care in patients who are mechanically ventilated for acute hypoxaemic respiratory failure.

6.3 Study Objectives

6.3.1 Primary objective

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

6.3.2 Secondary objectives

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

1) Tidal volumes
2) Duration of mechanical ventilation
3) Requirement for ECMO
4) Long-term mortality
5) Health Related Quality of Life
6) Safety
7) Cost-effectiveness in the NHS setting
8) Long term respiratory morbidity

7 STUDY DESIGN

7.1 Study Design

This is a randomised, allocation concealed, controlled, open, pragmatic clinical and cost effectiveness trial.

In PICO terms:

Population	Adult patients with acute hypoxaemic respiratory failure
Intervention	VV-ECCO$_2$R and lower tidal volume mechanical ventilation
Comparator	Standard care with conventional lung protective mechanical ventilation
Outcome	Mortality 90 days after randomisation

7.2 Internal Pilot Study

An internal 6-month pilot study in at least ten sites to confirm both recruitment and adherence assumptions that have contributed to study design will precede the main trial. The pilot will run from months 4-9 and will follow the processes described in the main study section below. Pilot data will come from a minimum of ten sites open to recruitment. The pilot will be used to confirm screening, consent procedures, recruitment rates, randomisation processes, data collection, protocol compliance and ensure follow-up processes run smoothly. Full details of the criteria for progression from the pilot study to the main study are given below.

If recruitment of 40 patients occurs more quickly than anticipated, progression to full trial may occur earlier than 6 months at the discretion of the Funder. The main parameters of interest, to guide the progress of the trial and inform the procedures to be used in its delivery, are: recruitment rates; adherence to the protocol-specified intervention; and separation of mechanical ventilation tidal volumes in the study groups. Participants enrolled in the pilot will be included in the analysis of the main study.

Progression to the full trial will be dependent on:

(i) Recruitment rate:
   a. Progression without major modification if at least 75% of recruitment target reached, with analysis and resolution of any identified barriers to successful recruitment.
   b. Progression with addition of further trial sites if between 40-75% of target reached, with detailed analysis of the screening log, protocol review and consultation with participants and refusers.
   c. Progression unlikely if less than 40% of target reached. A rescue plan will be proposed and this decision will be made by the TSC in association with the Health Technology Assessment secretariat.

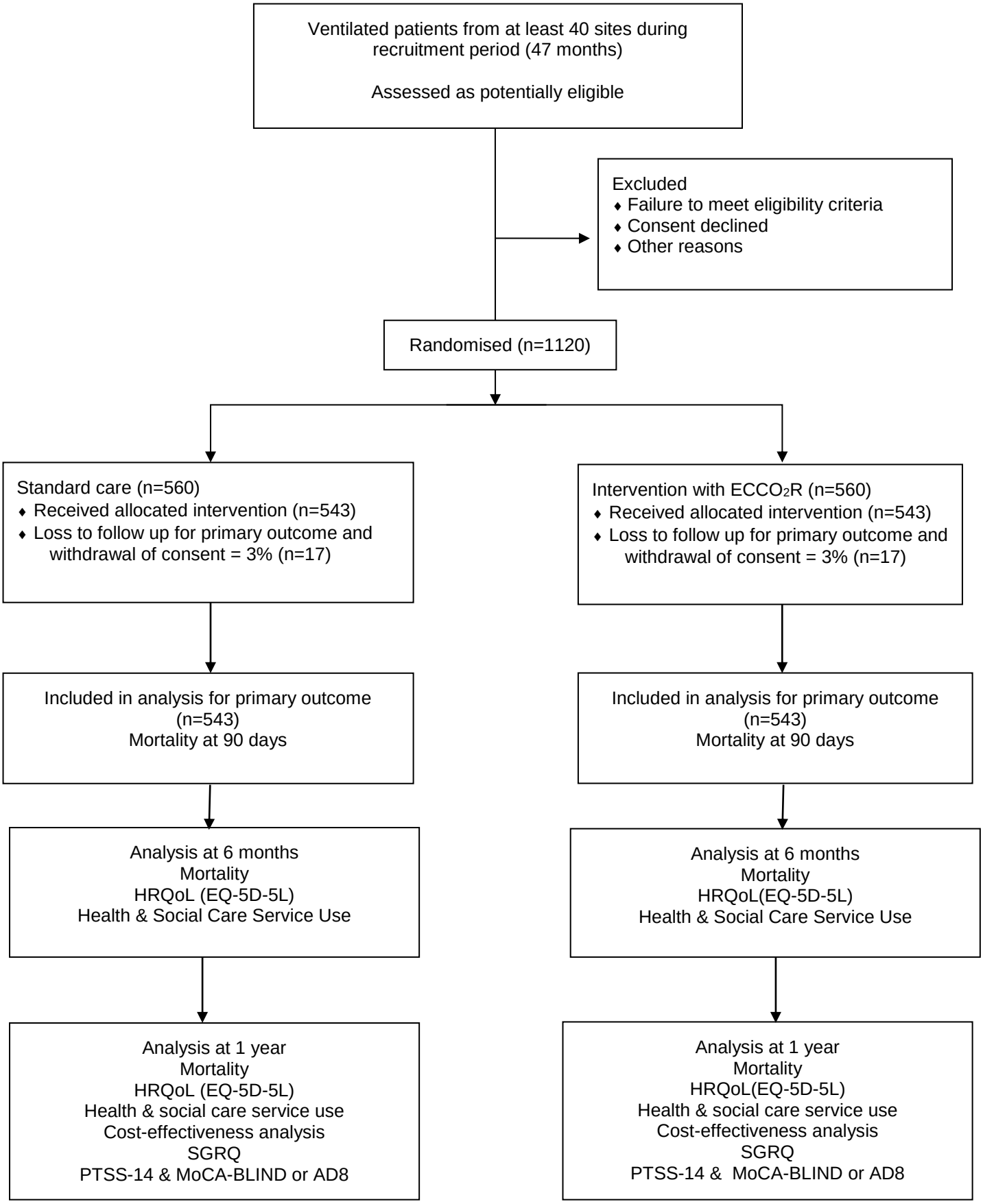
(ii) Separation, in terms of the intervention, between the two arms:
   a. Progression without major modification if there is at least 2ml/kg PBW tidal volume separation.
   b. If there is less than 2ml/kg PBW separation then progression will only be supported after a detailed analysis of the protocol and its implementation has identified where this can be improved with agreement from the HTA. This will include enhanced clinical supervision and training of the intervention providers

(iii) Follow-up assessments
   a. We will audit completeness of datasets and if below 95%, enhanced training for sites on CRF and dataset completion will be provided.
   b. If completion of datasets is less than 75% then progression will only be supported if there is a clear rescue plan that can be implemented to improve on this

compliance. This will include refining schedules to reduce the assessment burden, refining data collection tools and reviewing missing data procedures.

Study Schematic Diagram

Figure 1: Study Schematic



7.3 Study Timeline

The total trial duration will be 65 months.

We will open the first site within 3 months and aim to have at least 40 sites open within 9 months. The internal pilot will run between months 4-9. Following successful confirmation of recruitment rates the internal pilot will run seamlessly into the main trial. If necessary, additional study sites will be recruited.

The total recruitment period will last for 47 months with a follow up period of 12 months. There will be 3 months at the end for final data analysis, reporting and trial close down.

7.4 End of Study

The end of trial will be when database lock occurs for the final study analysis after 1120 participants have been randomised.

The study will be stopped early if mandated by the ethics committee, mandated by the Sponsor, mandated by regulatory authorities, recommended by the TSC or if funding ceases.

8 METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

8.1 Study Setting

The main trial will take place in at least 40 ICUs that are able to care for level 3 patients as previously defined (24).

The ICUs must provide evidence that they have:

- a proven track record of participating in ICU research.
- access to this population
- consultants in the ICU who have clinical equipoise for VV-ECCO$_2$R in this setting and agree to maintain trial allocation in patients randomised by their colleagues.

Staff must also demonstrate and document a willingness to comply with the protocol, standard operating procedures (SOPs), the principles of GCP (Good Clinical Practice), regulatory requirements and be prepared to participate in training. Experience with the management of VV-ECCO$_2$R will be addressed with a training package, with all sites having access to the equipment and the educational package. A list of study sites will be maintained in the TMF.

8.2 Eligibility Criteria

Patients will need to be assessed using the inclusion and exclusion criteria as set out below. Eligibility to participate in the trial will be confirmed by a medically qualified person who is named on the Delegation Log. The medical care given to, and medical decisions made on behalf of subjects will be the responsibility of an appropriately qualified treating physician.

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

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

8.2.1 Inclusion criteria

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

*Recommended on low tidal volume ventilation ≤ 6 ml/kg PBW
**Requires two ABG with a PaO_2/FiO_2 ≤ 20kPa separated by at least 6 hours. 48 hour duration to consent begins at the time of 2nd ABG demonstrating PaO2/FiO2 ratio ≤ 20kPa. Site will then have a further 8 – 24 hours to randomise and administer the intervention. The onset of hypoxaemia is from time of intubation and invasive ventilation.

(ABGs with PaO_2/FiO_2 ≥ 20kPa are permitted between the two trial inclusion ABGs).

8.2.2 Exclusion criteria

- Age < 16 years old
- Intubated and mechanically ventilated via an endotracheal or tracheostomy tube ≥ 7 days (168 hours) up to the time of randomisation
- Ability to maintain Vt ≤ 3ml/kg PBW while maintaining pH ≥ 7.2 as determined by the treating physician*
- Receiving, or decision to commence, ECMO in the next 24 hours.
- Mechanical ventilation using HFOV or APRV
- Untreated pulmonary embolism, pleural effusion or pneumothorax as the primary cause of acute respiratory failure.
- Acute respiratory failure fully explained by left ventricular failure or fluid overload (may be determined by clinical assessment or echocardiography/cardiac output monitoring).
- Left ventricular failure requiring mechanical support
- Contra-indication to limited systemic anticoagulation with heparin
- Unable to obtain vascular access to a central vein (internal jugular or femoral vein)
- Inferior vena cava filter (if using femoral vein catheter)
- Consent declined
- Treatment withdrawal imminent within 24 hours
- Patients not expected to survive 90 days on basis of premorbid health status
- DNAR (Do Not Attempt Resuscitation) order (excluding advance directives) in place
- Severe chronic respiratory disease requiring domiciliary ventilation (except for sleep disordered breathing)
- Severe chronic liver disease (Child Pugh >11)
- Platelet count < 40,000 mm^3 (Prior to catheter insertion)
- Previously enrolled in the REST trial
- Prisoners

* This exclusion criterion relates to whether a Vt ≤ 3ml/kg PBW could be achieved without the need for ECCO2R. A tidal volume ≤ 3ml/kg is unlikely to be achievable in most clinical scenarios without ECCO2R as it is approaching dead space ventilation.

There is no requirement to attempt to actually reduce the Vt to ≤ 3ml/kg PBW to demonstrate this – this decision is made on the judgement of the treating physician.

Our inclusion and exclusion criteria are designed to include those who reflect the general population of critically ill patients with acute hypoxaemic respiratory failure who may benefit from the therapeutic intervention and exclude patients who are unlikely to benefit due to their underlying condition or at increased risk of a complication from $ECCO_2R$.

8.2.3 Co-enrolment guidelines

Patients in the REST study 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 (25). The Clinical Trials Unit (CTU) should be informed if co-enrolment is being considered. Co-enrolment with any studies should be documented in the CRF.

8.3 Interventions

8.3.1 Intervention description

Table 1: Trial intervention in "TIDieR" format (26)

TIDieR item number	Item descriptor	Item
1	Brief name	REST (pRotective vEntilation with veno-venouS lung assisT in respiratory failure) Study
2	Why	Extracorporeal carbon dioxide removal ($ECCO_2R$) enables lower tidal volume mechanical ventilation (27).
3	What materials	Membrane lung and pump combined with a controller. A dual lumen venous catheter for vascular access.
4	What procedures	In the intervention arm a dual lumen catheter will be inserted into a central vein. $ECCO_2R$ is commenced and managed as per study manual. Tidal volumes are then reduced on mechanical ventilation to enable lower tidal volume ventilation.
5	Who provides	An appropriately trained clinician with the required competencies will insert the catheter. A member of the research team will commence $ECCO_2R$ which will then be managed by ICU nurses with the appropriate training.
6	How	Continuous bedside care.
7	Where	Participating general adult ICUs
8	When and how much	Commence within 48 hours of hypoxemia, and continue for at least 48 hours. Patients are then weaned off $ECCO_2R$ as per study manual. $ECCO_2R$ will be used for a maximum of 7 days as part of the study protocol. If continued longer this will be outside of the study protocol.
9	Tailoring	The device is weaned when patients are less hypoxaemic and have demonstrated signs of clinical improvement. The duration of this may vary between patients.
10	How well	The tidal volume separation and duration of $ECCO_2R$ will be reported.

The health technology being assessed is the use of VV-$ECCO_2R$ and lower tidal volume mechanical ventilation compared to standard care.

All aspects of intensive care and disease therapies will be according to standard critical care guidelines (See section 8.3.11). In both arms of the study we will allow a similar degree of hypercapnic respiratory acidosis as is currently practised within the UK ICU community based on our national survey (ICS State of the Art 2010).

- Ventilatory management in each study arm will be detailed in the study manual.
- Any mode of ventilation capable of delivering the prescribed tidal volume can be used as long as Vt and Pplat can be accurately monitored and adjusted accordingly.
- Recommended Positive End Expiratory Pressure (PEEP) will be based on the ARDSnet ARMA trial (6). (See appendix 2)
- Oxygenation will be titrated aiming for SpO_2 of 88%-95% or PaO_2 7-10kPa.
- Permissive hypercapnic respiratory acidosis aiming for a pH ≥ 7.2

8.3.2 Veno-venous Extracorporeal Carbon Dioxide Removal ($ECCO_2R$)

The study manual will provide detailed information regarding the insertion of the vascular catheter, set up and initiation and management of the VV-$ECCO_2R$ device. The manual will also detail the reduction in tidal volume and how to wean the device.

A summary is described below:

8.3.3 Insertion of the dual lumen catheter

The catheter is inserted preferentially into the right internal jugular or femoral vein using ultrasound guidance of needle and guide wire insertion (similar to the vascular approach used in renal replacement therapy). The catheter will be fixed in place and care of the catheter skin site will follow local infection control policy.

If the catheter is accidently dislodged or removed in the first 48 hours then a new catheter is reinserted and a total of at least 48 hours of lower tidal volume mechanical ventilation will be completed and continued until the weaning criteria are satisfied.

If dislodgement occurs after 48 hours of therapy and the weaning criteria have been satisfied then $ECCO_2R$ is discontinued and the patient is ventilated and weaned as per standard care. If the weaning criteria have not been met at time of dislodgement then a new catheter will be reinserted and continued until such time as weaning criteria have been met up to a total of 7 days.

8.3.4 Circuit

The $ECCO_2R$ device will be set-up according to the manufacturer instructions. Unfractionated heparin sodium by continuous infusion will normally be administered to achieve anticoagulation for the device. This is detailed in the study manual.

8.3.5 Management of VV-$ECCO_2R$

The VV-$ECCO_2R$ device will be attached to the catheter and the blood pump

commenced. The initial sweep gas flow will be set at a default of 1 l/min. Thereafter, the blood and sweep gas flows will be titrated according to the detailed instructions included in the study manual.

8.3.6 Reduction in tidal volumes

The underlying principle is to maximise CO_2 removal by $ECCO_2R$ to target:

- a tidal volume of ≤ 3ml/kg PBW and a Pplat ≤ 25cmH_20 whilst maintaining the arterial pH ≥ 7.20

- Arterial blood gases should be monitored and if the arterial pH is < 7.20 no further tidal volume reductions should be attempted. Respiratory rate can be increased accordingly to a maximum of 35/min to allow tidal volume reduction.

- If a respiratory alkalosis develops (arterial pH > 7.45) it is recommended the respiratory rate is decreased incrementally

- Mandatory ventilation is mandated in the first 48 hours to ensure lower tidal volume mechanical ventilation is delivered (Vt ≤ 3ml/kg PBW)

8.3.7 VV-$ECCO_2R$ Weaning

After 48 hours and daily thereafter, the patient will be assessed to determine whether criteria to progress to $ECCO_2R$ weaning have been met. This is detailed in the study manual.

If the criteria are not all met on daily assessment then $ECCO_2R$ should be continued for a maximum of 7 days aiming for tidal volumes of ≤ 3 ml/kg PBW in either mandatory ventilation or pressure support ventilation. It is recognised at this stage that spontaneous breath tidal volumes may be difficult to limit even with minimal pressure support.

After 7 days $ECCO_2R$ should be discontinued. If $ECCO_2R$ is continued at the discretion of the treating physician for a longer period, this is outside the study protocol and would form part of clinical care.

Weaning from the $ECCO_2R$ device will be detailed in the study manual. Once weaned the cannula will be removed as per local policy on removing central venous lines.

8.3.8 Intervention discontinuation

Therapy will be terminated if:
1) the patient's legal representative requests withdrawal from the study
2) there is a safety concern about the therapy such that withdrawal is mandated
3) $ECCO_2R$ therapy has been weaned
4) 7 days post randomisation
5) escalation to ECMO occurs
6) discontinuation of active medical treatment occurs
7) the patient dies

Following cessation of therapy, the $ECCO_2R$ controller will be cleaned according to the local Trust's Infection Control Policy and in accordance with manufacturer's instructions.

8.3.9 VV-ECCO$_2$R Equipment

ICUs that participate in the trial will be supplied with at least one ECCO$_2$R device and the required consumables for trial subjects. The manufacturer will be responsible for delivery and maintenance of the device. Centres will not commence the trial until regulatory approvals are in place and the appropriate training has taken place for the site staff. The site will also agree that the equipment will be removed if there are violations in its use and prohibit the use of the trial-specific consumables for non-trial patients.

The device will be stored within access of the ICU where it is to be used. Each patient will have individual non-reusable consumables that will be provided in sterile packaging by the company. The device will only be used as part of the study protocol in compliance with its CE mark.

8.3.10 Training

A clinical training group will be responsible for the set up and training of staff at sites. This will be made up of experts in extra-corporeal technology, research nursing staff and VV-ECCO$_2$R device support staff. Previous level of experience of VV-ECCO$_2$R will be determined at the sites. Sites may not have had experience with the use of ECCO$_2$R before so the clinicians will be trained on how to operate the device with the assistance of the ECCO$_2$R device support staff. Instructional material will be provided to trial sites. The group will provide training on the study manual and facilitate training by the manufacturers on the VV-ECCO$_2$R device at the site

8.3.11 Concomitant / Standard care

Mechanical Ventilation
It is recommended that patients are mechanically ventilated according to best practice. Ventilation according to the ARDSNetwork ARMA trial, which demonstrated a reduction in mortality using a tidal volume of 6 ml/kg PBW is recommended (6). Target tidal volumes will be ≤ 6 ml/kg PBW to maintain a plateau pressure ≤ 30cmH_2O. To ensure compliance with standard care in the main trial we will audit ventilator parameters every 3 months and give feedback to sites.

Neuromuscular Blocking Drugs
Patients in both the intervention and control arm can receive neuromuscular blocking drugs (NMBD) at any stage to ensure patient-ventilator synchrony. This is in keeping with recent evidence that suggests NMBD are of benefit in early hypoxaemic respiratory failure due to ARDS (8).

Refractory Hypoxaemia
If the treating physician is concerned about hypoxaemia, interventions including prone positioning or referral for consideration of extracorporeal membrane oxygenation (ECMO) can be applied in either arm of the trial as per standard care in the UK.

Intravenous Fluid and Blood Therapy
It is recommended that patients will be managed with a conservative fluid balance strategy according to best evidence for patients with hypoxaemic respiratory failure (28). Blood transfusions should be in keeping with the best practice of a restrictive transfusion policy (29). Platelet transfusion at the discretion of the clinical team is allowed to achieve a platelet count of at least 40,000 mm^3 to facilitate the insertion of

the venous catheter for $ECCO_2R$ as well as maintain a platelet count to allow systemic anticoagulation.

Extracorporeal Carbon Dioxide Removal
$ECCO_2R$ is an unproven therapy in hypoxaemic respiratory failure and its use is discouraged as a salvage therapy for standard care. The crossover and use of the device in the non-interventional arm will be considered a protocol violation. Persistent violations may result in termination of the trial at that site.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

All cause mortality 90 days after randomisation

8.4.2 Secondary Outcome Measures

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

8.4.3 Exploratory Outcome Measures

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

8.5 Sample Size

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

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

1. Data from the Intensive Care National Audit & Research Centre (ICNARC) case mix programme (CMP) for UK intensive care patients. The unpublished ICNARC data from the CMP for the year 2012 was compiled from 133,266 admissions from 203 adult critical care units in England, Wales and Northern Ireland. For patients with a PaO_2/FiO_2 ratio < 20kPa the ICU mortality was 40.7% and the hospital mortality was 48.8%.

2. Data from the NIHR HTA funded OSCAR trial (30). This was a recent large randomised controlled trial on high frequency oscillatory ventilation (HFOV) in patients with respiratory failure. The 30-day mortality in the control group in the OSCAR trial was 41.1%. These patients received conventional ventilation with a tidal volume of 6-8ml/kg PBW and had an average PaO_2/FiO_2 ratio of 15kPa.

We have assumed 90-day control group mortality will be at least equivalent to 41%. We have used the effect size of one of the few interventions to reduce mortality in patients with hypoxaemic respiratory failure. The ARDSNet ARMA trial demonstrated a 9% absolute risk reduction in patients with hypoxaemic respiratory failure secondary to ARDS with lung protective ventilation (6). Our hypothesis is that we can extend the benefits of more protective lung ventilation with the use of $ECCO_2R$ (14). Loss to follow up in UK critical care trials is low. We know this is approximately 3% from previously published research as well as from the experience of our team in managing large critical care trials in the UK (30-32).

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

8.6 Recruitment

8.6.1 Screening procedure

Sites will be provided with posters to be used to highlight the study is on-going at their site.

All mechanically ventilated patients in the ICU will be screened daily each morning for eligibility. Patients clinically judged to have hypoxaemic respiratory failure will be screened against the inclusion and exclusion criteria. Eligible patients will then be discussed with their treating ICU physician to confirm their agreement with trial enrolment and willingness to follow the treatment strategy allocated in either arm of the trial. A screening log will be maintained which will include data on the numbers of patients meeting eligibility criteria for the trial but not entered into the trial. A fully anonymised minimal dataset will be recorded on these patients (age, gender, APACHE II score, worst P/F ratio at time of assessment, reasons for non-enrollment and vital status). APACHE II score and vital status will be collected using anonymised linkage to the ICNARC database through a defined CMP number. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement (33)

8.6.2 Informed consent procedure

It is the responsibility of the Principal Investigator (PI) (or designee) to ensure that written informed consent/advice is obtained for each participant prior to entry into the trial. Consent/advice may be obtained by the PI; an appropriately trained Research Nurse; or medically trained investigator. The PI (or designee) taking informed consent/advice must be GCP trained, suitably qualified and experienced and have been delegated this duty by the Principal Investigator on the delegation log.

Where patients' representatives require further clarification about the benefits and risks of participating, this will be provided by either the research team or an independent senior physician (one will be nominated in advance for each trial site).

Patients will be unable to give informed consent due to the effects of sedation, infection, delirium and mechanical ventilation; consent/advice will therefore be obtained in line

with the legal requirements for obtaining advice in patients without capacity in England and Wales (Mental Capacity Act 2005), and consent in Scotland (Adults With Incapacity (Scotland) Act 2000). Northern Ireland follows common law; for the purposes of the REST trial processes used in England and Wales will be used in Northern Ireland.

Personal Consultee (England, Wales and Northern Ireland)
The researcher will seek advice from a Personal Consultee (who may be a relative, partner or friend of the participant). This should normally take place during a face-to-face meeting. An authorised staff member/researcher will describe the REST trial to the individual, and provide them with a Covering Statement, Information Sheet and Personal Consultee Declaration (England/Wales and Northern Ireland). The researcher will seek their views about whether the patient should take part in the study. They will be asked about their opinion of the wishes and feelings of the patient if they had capacity.

After the researcher has checked that the information sheet is understood, the researcher will invite the Personal Consultee to sign the form and will then countersign it. A copy of the form should be placed in the patient's medical notes and a copy filed in the ISF.

If the Personal Consultee is not available at site, the researcher may contact the Personal Consultee by telephone and seek verbal agreement. This verbal agreement will be recorded in the Consultee Telephone Agreement Form. The Consultee Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone advice. This witness may be a member of the site study team or site medical staff. A copy of the Consultee Telephone Agreement Form should be placed in the patient's medical notes and a copy filed in the ISF. Written agreement will then be obtained as soon as possible.

Nearest Relative/Guardian or Welfare Attorney (Scotland)
The researcher will seek consent from a Nearest Relative/Guardian or Welfare Attorney (who may be a relative, partner or friend of the participant). This will usually take place during a face-to-face meeting. An authorised staff member/researcher will describe the REST trial to the individual, and provide them with a Covering Statement, Information Sheet and Consent Form for Nearest Relative/Guardian or Welfare Attorney (Scotland). The researcher will seek their views about whether the patient should take part in the study. They will be asked to give their consent based on their opinion of the wishes and feelings of the patient if they had capacity

After the researcher has checked that the information sheet is understood, the researcher will invite the Nearest Relative/Guardian or Welfare Attorney to sign the form and will then countersign it. A copy of the form should be placed in the patient's medical notes and a copy filed in the ISF.

If there is no Nearest Relative/Guardian or Welfare Attorney available at site, the researcher may contact the Nearest Relative/Guardian or Welfare Attorney by telephone and seek verbal agreement. This verbal agreement will be recorded in the Consultee Telephone Agreement Form. The Consultee Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone consent. This witness may be a member of the site study team or site medical staff. A copy of the Consultee Telephone Agreement Form should be placed in the patient's medical notes and a copy filed in the ISF. Written agreement will then be obtained as soon as possible.

These processes have worked successfully in similar large multicenter UK studies

previously (e.g. OSCAR, ABLE and BREATHE).

Approval by a Registered Medical Practitioner (RMP):
England, Wales and Northern Ireland
In the event that there is no Personal Consultee for sites in England, Wales and Northern Ireland, authorisation to randomise the patient will be sought from an RMP (a doctor unrelated to the study conduct). The RMP will be informed about the trial by a member of the research team and given a copy of the Registered Medical Practitioner Form (England/Wales and Northern Ireland) and a copy of the Covering Statement, Information Sheet and Personal Consultee Declaration (England/Wales and Northern Ireland). If the RMP decides that the patient is suitable for entry into the study they will be asked to complete the relevant authorisation form. A copy of the authorisation form should be placed in the patient's medical notes and a copy filed in the ISF. In the event that a Personal Consultee is identified after RMP advice is obtained, the above process for Personal Consultee Declaration will be followed and all advice forms will be filed as instructed above.

Scotland
For sites in Scotland where no Nearest Relative/Guardian or Welfare Attorney is available it will not be legally possible to enroll the patient (specific to the Adults with Incapacity Act Scotland for non-CTIMP trials).

Patient consent to continue
Once the participant has recovered from the condition / treatment causing incapacity, and has been free from sedative medications for more than 24 hours they will be approached to obtain permission to continue in the study.
The consent to continue process will include: assessment and documentation of capacity; providing the Patient Information Sheet and Consent Form for Participant with Recovered Capacity; allowing sufficient time for the patient to understand the material and ask questions; obtaining written informed consent. If the patient agrees to continue in the study they will be asked to sign the Consent Form for Participant with Recovered Capacity Form which will then be counter signed by a member of the research team. A copy of the Participant with Recovered Capacity Form will be filed in the ISF and a copy filed in the patient's medical notes. If the participant declines on-going participation in the study no further follow-up will take place. Data collected up until that point will be anonymised before returning to the co-ordinating centre. In the rare event that the patient does not regain capacity or the staff have been unable to obtain consent to continue, the consent from the Personal Consultee or Nearest Relative/ Guardian or Welfare Attorney or Registered Medical Practitioner will continue.

8.6.3 Withdrawal of consent

Participants may withdraw or be withdrawn (by their Personal Consultee/Nearest Relative/Guardian or Welfare Attorney or the intensive care consultant responsible for their care) from the study at any time without prejudice. In the event that the participant is withdrawn, the treating clinician responsible for their care will determine the safest and most appropriate way to continue the care outside of the study protocol.
In the event of a request to withdraw from the study, the researcher will determine which elements of the study are to be withdrawn from the following possibilities and this will be documented:

- The application of extracorporeal carbon dioxide removal

- On-going data collection during hospital admission
- Confirmation of vital status
- Contact for follow-up questionnaires

In the event that the request is to withdraw from all elements of the study, only anonymised data recorded up to the point of withdrawal will be included in the study analysis.

9 METHODS: ASSIGNMENT OF INTERVENTIONS

9.1 Randomisation Procedure

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

Randomisation will be stratified by recruitment centre.

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

The research team will then ensure that the clinical team are informed which treatment this process has allocated. They will liaise with the clinical team as required to ensure that the allocated treatment is administered. If allocated VV-$ECCO_2R$, this should ideally be commenced within 8 hours of randomisation.

9.2 Blinding

Only the allocation of the intervention will be concealed; once assigned to the standard care or intervention group the interventions will be unblinded to the trial participant's representative (and to the participant on regaining capacity), research team, care providers, data analysts and outcome assessors. By the nature of the intervention it will not be possible to blind clinicians to whether a participant has been randomised to $ECCO_2R$ or standard care.

10 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

10.1 Data Quality

The Chief Investigator/Clinical Lead (CI/CL) and NICTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Within the NICTU the clinical data management process is governed by Standard Operating Procedures (SOPs), which help ensure standardisation and adherence to International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines and regulatory requirements. Data is to be entered onto the electronic database as per the CRF entry timelines.

On-site monitoring visits during the trial will check; the accuracy of the data entered into the CRF, entries against source documents alongside adherence to the protocol, trial specific procedures and Good Clinical Practice (GCP). This monitoring will be carried out as per the trial specific Monitoring Plan.

Changes to data will be recorded and fully auditable. Data errors will be documented and corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range or inconsistent, or protocol deviations, based on data validation checks programmed into the clinical trial database.

An independent Data Monitoring & Ethics Committee (DMEC) will be convened for the study to carry out reviews of the study data at intervals during the study.

10.2 Data Collection

10.2.1 Study Visits and Procedures

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

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

- Patient demographics (date of birth, gender, measured height)
- ICNARC Case Mix Programme (CMP) number
- SICSAG number
- Date/time of consent and randomisation
- Date and time of ICU admission
- Admission diagnostic category
- Assessment of functional status
- Presence of ARDS and aetiology
- Date/time of onset of mechanical ventilation
- The Acute Physiology and Chronic Health Evaluation score (APACHE II)
- PaO_2/FiO_2 ratio (Qualifying PaO_2/FiO_2 ratios including date/time)
- Date and time of worst PaO_2/FiO_2 ratio
- Determinants of Sequential Organ Failure Assessment (SOFA) score
- Ventilation parameters including but not limited to: Mode of ventilation, minute

volume, RR, mean airway pressure, plateau pressure, PEEP
- Arterial blood gas including but not limited to FiO_2, PaO_2, $PaCO_2$, pH
- Date/time onset of $ECCO_2R$ therapy (from commencement of CO_2 removal)
- Use of adjunctive therapies including NMBD and prone position
- Echocardiography parameters including but not limited to ventricular size and function and tricuspid annular plane systolic excursion (TAPSE).

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

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

Day 1 and 2:
Echocardiography parameters including but not limited to ventricular size and function and tricuspid annular plane systolic excursion (TAPSE).

Day 3 and 7:
- Determinants of SOFA score

28 Days:
- Adverse Events

6 months:
- EQ-5D-5L (Post or telephone)
- Patients use of health and social care resources collected by resource logs

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

The following data will also be collected
- Date of discontinuation of $ECCO_2R$ and reason
- Date of discontinuation of mechanical ventilation (unassisted breathing)
- Date of critical care discharge
- Date of hospital discharge
- Date of death

Discharge from critical care is defined as first discharge to a medical ward in the hospital or another hospital; a transfer between ICUs is not considered a discharge

from critical care. Hospital discharge is the first date that the patient is discharged to home/ community, a transfer between hospitals is not considered as a hospital discharge.

Unassisted breathing i.e. no ventilatory support is defined as: extubated with supplemental oxygen, or room air, or open T-tube breathing, or tracheostomy mask breathing, or CPAP ≤ 5 cm H_2O without pressure support for a calendar day. Patients receiving pressure support via non-invasive ventilation will be defined as receiving ventilatory support (except for sleep disordered breathing).

VFDs to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.
Duration of ventilation will be counted from recruitment to the end of the last period of assisted breathing

10.2.2 Follow Up Visits and Procedures

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

The CTU will also collect mortality data at 1 and2 years post randomisation using the Health and Social Care Information Centre (HSCIC).

10.3 Study Instruments

10.3.1 EQ-5D-5L

The EQ-5D-5L is a generic preference-based measure of health, which provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with 5 levels of severity (34). Responses are converted to an overall utility score which will be used for the calculation of quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale (VAS) where 0 represents the worst imaginable health state and 100 the best imaginable health state. It is recommended by NICE (NICE 2013) for use in economic evaluations.

10.3.2 Health and Social Care Service Use Questionnaire

A resource use questionnaire and log sheet has been developed specifically for the REST study. The questionnaire will be administered at 6 months and 12 months after randomisation and will capture the patients' use of health services, such as community, social, hospital and care services as well as oxygen usage. The log sheet will be given to patients at discharge and 6 months to record their contacts prospectively.

10.3.3 St George's Respiratory Questionnaire

The SGRQ questionnaire has 50 items with 76 weighted responses. It has good discriminative and evaluative properties and is responsive to therapeutic trials. The SGRQ has been used in a range of disease groups including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis, and in a range of settings such as randomised controlled therapy trials and population surveys. There is a large amount of literature concerning the use of the questionnaire in many settings, including normal values (35).

10.3.4 The Montreal Cognitive Assessment (MoCA) Blind

The Montreal Cognitive Assessment (MoCA) - BLIND is an adapted version of the original MoCA, a rapid screening instrument for mild cognitive dysfunction. The MoCA-BLIND assesses different cognitive domains: attention and concentration, memory, language, conceptual thinking, calculations, and orientation.

10.3.5 AD8

The AD8 is an 8-item questionnaire that distinguishes between people who have dementia and people who don't.

10.4 Participant Retention and Follow-up

Participant survival after discharge from hospital will be determined using the Health and Social Care Information Centre if available in that region or by contacting the GP. This will be undertaken centrally by NICTU staff.

After being informed of a participant's discharge, the Coordinating Centre (NICTU) will send a card and a voucher thanking them for their participation in the study and reminding them that the Coordinating Centre will be back in touch to request that questionnaires are completed over the course of the following year. All survivors will be followed up by postal questionnaires at 6 months and one year after randomisation. If postal follow-up questionnaires are not returned, a maximum of two telephone contacts will be made to the study participant; the first call will check that the questionnaire has been received and the participant is happy to complete it. If necessary a second copy of the questionnaire will be sent. In the event of non-return one further telephone contact will be made and the outcome data collected over the telephone where possible. Patients' consent will be obtained to contact them should they not return their questionnaire.

In addition, the Coordinating Centre will contact patients by phone one year after randomisation to complete the PTSS and MoCA-Blind telephone questionnaire. In the event that the patient does not feel able to complete the MoCA-Blind questionnaire, they will be asked if a relative, partner or friend is available to act as proxy to complete the AD8 questionnaire in place of the MoCA-Blind questionnaire.

Any deaths after discharge from hospital will be identified to avoid sending questionnaires or attempting telephone contact to patients who have died. Study participants will be asked to let the Coordinating Centre know if they move house at any time after hospital discharge; HSCIC will enable us to locate any who move house without informing the Coordinating Centre.

10.5 Data Management

The PI (or designee) will collect all data and record this in the CRF. Each participant will be allocated a unique Participant Study Number at trial entry, and this will be used to identify him or her on the CRF for the duration of the trial. Data will be collected from the time of trial entry until hospital discharge. Trial data will be entered onto a CRF and processed electronically as per CTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP). Data queries will be raised electronically. Where clarification from site staff is required for data validations or missing data, site staff will respond to data queries ensuring that amendments are made as required. Trial questionnaires data will be entered by CTU staff. If the participant is transferred to another hospital the PI or designated member of the site study team will liaise with the receiving hospital to ensure complete data capture as per CRF instruction. If this is not possible, the primary outcome must be collected as a minimum. If the hospital that the participant is transferred to is a site that is participating in the trial and the patient has been randomised to the trial intervention, then $ECCO_2R$ should be continued for the full 7 days if appropriate, or for a minimum of 48 hours duration.

10.6 Data Analysis

10.6.1 Analysis population

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

10.6.2 Statistical methods

A detailed Statistical Analysis Plan (SAP) will be written for both the pilot trial and the main trial by the trial statistician and approved by the independent DMEC prior to any interim analysis.

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

For the primary outcome and other dichotomous outcomes, risk ratios and 95% confidence interval (CI) will be calculated. The primary outcome of 90 day mortality will be analysed using chi-square and a secondary analysis using logistic regression to adjust for important covariates will also be carried out. The comparison of continuous outcomes between the two groups will be investigated using analysis of covariance, adjusting for other covariates where appropriate. Time-to-event outcomes will be analysed by survival methods and reported as hazard ratios with 95% CI. The intention-to-treat basis analysis will use a significance level of <0.05. Sensitivity analysis will be performed for the primary outcome excluding the first two intervention arm patients at each site in order to address potential learning effects. This would be explored further using a model based approach (36).

An independent statistician on the DMEC will conduct an interim analysis for the primary outcome measure before the recruitment of 560 patients. Using the chi-square statistic (mortality by treatment group), a p value less than 0.001 will be used according to the Haybittle-Peto stopping rule (37).

10.6.3 Health economics evaluation

A cost-effectiveness analysis will be undertaken to compare the costs and outcomes associated with VV-$ECCO_2R$ to those associated with standard care at two time points. The initial, within-trial analysis will be based on the costs and outcomes measured within the one-year study period, while the second model-based analysis will

extrapolate the cost and outcomes over a lifetime horizon. Both analyses will estimate the cost per quality adjusted life year (QALY) gained. They will adhere to the National Institute for Health and Care Excellence's (NICE) guide to methods of technology appraisal (38), where appropriate. The analyses will be performed from the perspective of the National Health Service (NHS) and personal social services (PSS). For the within-trial analysis, patients' use of health and social care resources over the study period will be collected from baseline until one year. This will include duration and level of critical care received and hospital ward length of stay, therapeutic procedures received (including transfusions), outpatient visits and patient contacts with primary care. Resource use associated with the primary admission will be collected using the case report form. Health and social care service use following discharge to 12 months will be captured via self-completed resource questionnaires at 6 and 12 months. Log sheets will be provided at discharge and 6 months to help patients keep track of their service use. Costs will be calculated by attaching appropriate unit cost from publicly available sources (e.g. Department of Health National Schedule of Reference Costs). Utilities for the calculation of the QALYs will be gathered using the EQ-5D-5L administered at 6 months and one year (34). These will be completed by the patients where possible and by a proxy where not.

Standard methods will be used to explore and display uncertainty in the cost-effectiveness data including scatterplots on the cost-effectiveness plane and cost-effectiveness acceptability curves (CEAC). Sensitivity analysis will be performed to assess the robustness of the cost-effectiveness results to changes in key parameters (including the cost of the VV-ECCO$_2$R device). A decision-analytic model will be developed in order to estimate the lifetime cost-effectiveness. The model will be populated by both primary cost and outcome data derived from the within-trial analysis and data extracted from secondary sources. The model structure will be informed by a review of the literature and will follow accepted guidelines for good practice in decision-analytic modelling (38, 39). Probabilistic sensitivity analyses will be undertaken to investigate uncertainty surrounding the estimates of lifetime costs and outcomes of VV-ECCO$_2$R and standard care.

10.6.4 Subgroup analyses

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

1) Presence of ARDS prior to randomisation
2) Baseline PaO_2/FiO_2 ratio prior to randomisation
3) Baseline Plateau Pressure prior to randomisation
4) Volume of $ECCO_2R$ participants at center
5) Vasopressor requirement prior to randomisation
6) Baseline $PaCO_2$ prior to randomisation
7) Baseline driving pressure prior to randomisation
8) Baseline risk of death score (Apache II) quintiles prior to randomisation.

10.6.5 Missing data

Every effort will be made to minimise missing baseline and outcome data in this trial. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate.

11 METHODS: ADVERSE EVENTS: DEFINITION, RECORDING AND REPORTING

11.1 Definition of Adverse Events

The European Commission guidance document "Guidelines on Medical Devices – Clinical Investigations – Serious Adverse Event Reporting " MEDDEV 2.7/3 provides the definitions given in table 2. This is based on the International Organisation for Standardisation (ISO) published revised standard on good clinical practice requirements for medtech clinical investigations, ISO 14155:2011 "Clinical Investigation of medical devices for human subjects" – Good clinical practice.

Table 2: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. **NOTE 1**: This includes events related to the investigational device or the comparator. **NOTE 2**: This includes events related to the procedures involved (any procedure in the clinical investigation plan). **NOTE 3**: For users or other persons this is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. **NOTE 2**: This includes any event that is a result of a use error or intentional misuse.
Serious Adverse Event (SAE)	Any adverse event that: a) Led to a death b) Led to a serious deterioration in health that either: 1) resulted in a life threatening illness or injury, or 2) resulted in a permanent impairment of a body structure or a body function, or 3) resulted in patient hospitalisation or prolongation of existing hospitalisation, or 4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

	c) Led to fetal distress, fetal death or a congenital abnormality or birth defect. **NOTE 1**: This includes device deficiencies* that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system. **NOTE 2**: A planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. **NOTE**: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the list of expected adverse events (See appendix 3)

*Device Deficiency: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

11.2 Adverse Event Reporting

11.2.1 Adverse Event Reporting Period

The AE reporting period for the trial begins upon enrolment into the trial and ends 28 days following randomisation.

11.2.2 Adverse Event Reporting

The PI or their delegated investigator is responsible for recording and reporting of AEs observed during the study period.

It is important that all adverse events in both the control standard care and intervention groups are reported.

As this study is recruiting in a population that is already in a life-threatening situation it is expected that many of the patients will experience events that are in keeping with the patient's underlying condition rather than being related to the trial. A list of expected AEs related to $ECCO_2R$ is provided in appendix 3. Consequently events which occur during the 7-day intervention period following randomisation and which are listed in appendix 3 even if occurring as a result of the patient's underlying condition will be reported as an AE. Other events occurring as a result of the patient's underlying condition will not be reported as an AE.

The PI must assess severity, seriousness, causality, and expectedness for any AEs in keeping with regulatory requirements (see below 11.3 - 11.6).

The word "**event**" is used for untoward medical occurrences not related to the investigational device. The word "**effect**" is used for occurrences related to or caused by the investigational device (see table 2 above).

The investigator should attempt, if possible, to establish a diagnosis based on the subject's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the investigator should report the diagnosis as the AE, rather than reporting the individual symptoms. All AEs should be treated appropriately.

The appropriate event report page in the CRF will be completed and submitted to the Trial Coordinating Centre to meet the timelines stated in the CRF Submission Schedule. All AEs should also be recorded in the patient medical notes.

11.2.3 Serious Adverse Event Reporting

All events meeting the definition of a serious adverse event (SAE) will be entered onto the Serious Adverse Event reporting form and submitted to the NICTU within 24 hours of the investigator becoming aware of the event.

The PI should not wait until all information about the event is available before notifying the CTU of an SAE. Information not available at the time of the initial report must be documented on a follow up SAE Form. Follow up information should be sought and submitted as it becomes available. The follow up information should describe whether the event has resolved or persists, if and how it was treated and whether the patient continues on the study or has been withdrawn from treatment.

Once received, seriousness, causality and expectedness will be confirmed by the Chief Investigator (or delegated clinical lead).

Unanticipated Serious Adverse Device Effect (USADE)
SAEs that are deemed to be related to the study device or any of the research procedures and are unanticipated will be notified to the Research Ethics Committee (REC) within 15 days of the NICTU becoming aware of the event.

11.3 Grading of Severity of Adverse Events

The PI or designee will record the severity using the following criteria.

Table 3: Grading of severity for Adverse Events

Category	Condition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health
Life Threatening	A reaction that has life threatening consequences; urgent intervention indicated.
Fatal	A reaction that results in death.

11.4 Assessment of Seriousness

The PI or designee should make an assessment of seriousness i.e is this an event that fulfils the criteria as defined in Table 2.

11.5 Assessment of Causality

The PI or designee should make an assessment of the **causality** (i.e. relationship to trial device) for each event. Events which are possibly, probably or definitely related to the device are reported as related. This will be determined as follows:

Table 4: Assessment of Causality for Adverse Events

Relationship to study intervention	Description
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably	

	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after using the device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
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 treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

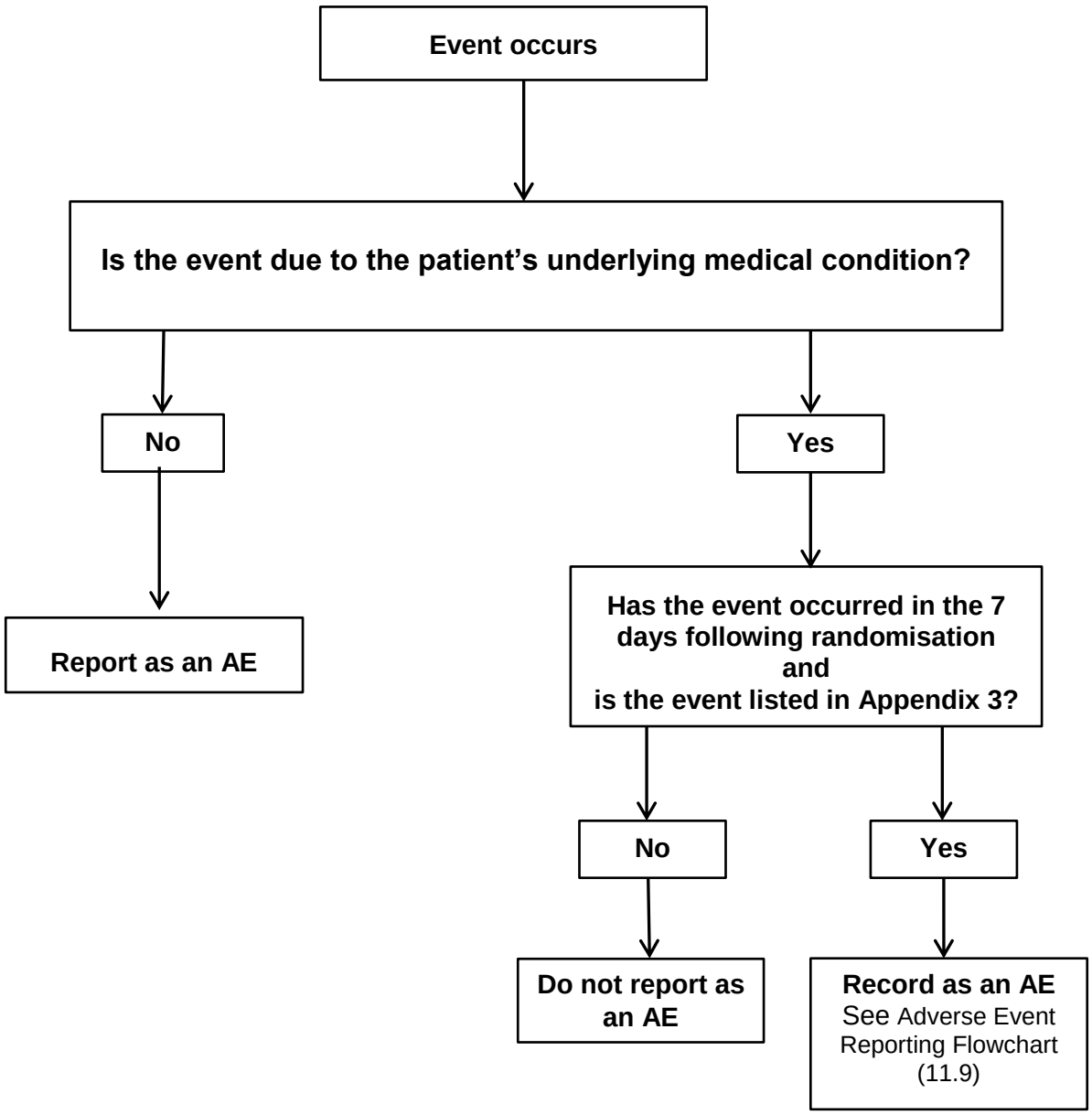
11.6 Assessment of Expectedness

The PI or designee should make an assessment of expectedness for each SAE regardless of the causal relationship to the trial device. The evaluation should be performed using the list of expected adverse events in Appendix 3.

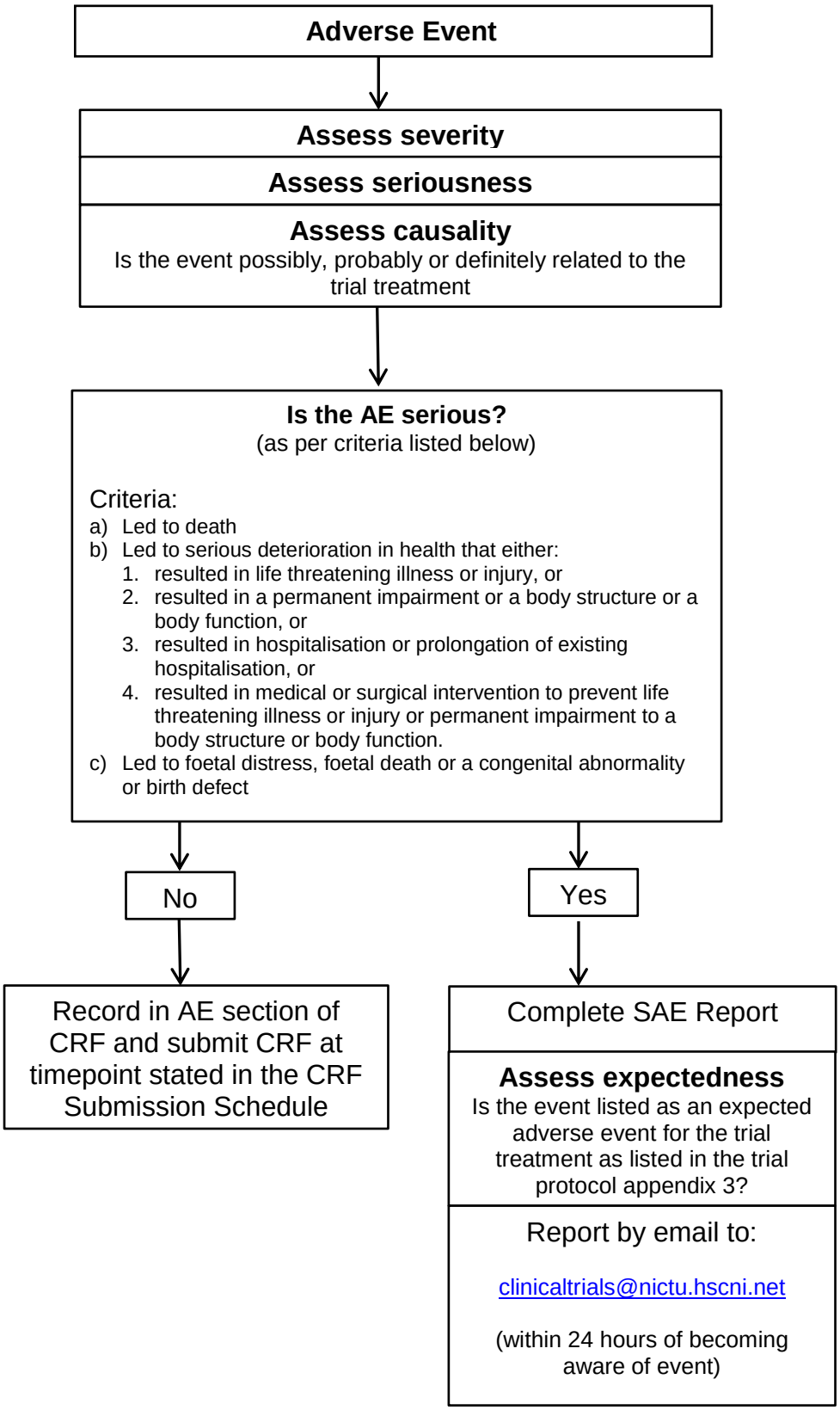
11.7 Follow-up of Adverse Events

All AEs assessed by the PI or designee as possibly, probably or definitely related to the device and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). The CRF should be updated with the date and time of resolution or confirmation that the event is due to the patient's illness as soon as this information becomes available

11.8 Adverse Event: Reportable Events Flowchart



11.9 Adverse Event: Reporting Flowchart



11.10 Recording and Reporting of Urgent Safety Measures

If the PI, designee, or a member of study staff become aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they should report the urgent safety measure immediately to the CTU by phone and follow this up in an email to clinicaltrials@nictu.hscni.net

The CTU will report the urgent safety measure immediately to the Sponsor using the dedicated email address (clinical.trials@belfasttrust.hscni.net), and will liaise with the Sponsor and site to implement immediate procedures to eliminate any hazard. The CTU will report immediately by phone to the study REC and will follow this up with an email written notice within 3 days of becoming aware of the urgent safety measure. The email notice will state the reason for the urgent safety measure and the plan for further action.

The PI or designee should respond to queries from the CTU immediately to ensure the adherence to these reporting requirements.

12 DATA MONITORING

12.1 Data Access

The agreement with each PI will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Agreement / consent from patients/Personal Consultee/Nearest Relative/Welfare Attorney as appropriate for this will also be obtained. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. On-site monitoring visits will be conducted in accordance with the trial monitoring plan. On-site monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP). The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating site, an initiation meeting will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. On-site monitoring visits during the trial will check the accuracy of data entered into the CRF against the source documents, adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up.

The PI or designee should ensure that access to all trial related documents including source documents are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

The close out procedure at each site will commence once the final patient enrolled has completed all site follow-up required by the protocol.

13 REGULATIONS, ETHICS AND GOVERNANCE

13.1 Sponsorship

The Belfast Health and Social Care Trust will act as sponsor for the study.
Sub-contracts delegating responsibilities to research sites will be established using our standard contracting processes with NHS organisations.

13.2 Regulatory and Ethical Approvals

This is an academic study of a marketed medical device for which there is a labeled indication. As the trial will be employing a medical device for a purpose for which it has approval, and the device has a CE mark, approval from the Medicines and Healthcare products Regulatory Agency (MHRA) will not be required. The REST study is not a Clinical Study of an Investigational Medicinal Product, and thus is not governed by the Medicines for Human Use (Clinical Trials) Regulations 2004.

The trial will require research and ethical (REC) approval and NHS permission. We will apply separately for ethical approval to a multi-centre research ethics committee (MREC) flagged for trials involving patients without capacity in Scotland and England. The ethics application made by the Chief Investigator will cover all collaborating sites. The application to the REC and the relevant NHS R&D offices will be made through the Integrated Research Application System (IRAS).

The trial protocol was prepared in compliance with the SPIRIT 2013 statement (40). The trial will be registered.

13.3 Protocol Compliance and Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee. Protocol compliance will be monitored by the Trial Monitor at site visits. Any deviations from the protocol will be fully documented in in the CRF.
All protocol amendments will be undertaken in accordance with the regulatory requirements. Substantial changes to the protocol will require ethics committee approval/favourable opinion, and industrial partner agreement prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients.

13.4 Good Clinical Practice

The study will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki, those in the Medical Research Council's Good Clinical Practice and the Department of Health's Research Governance Framework

13.5 Patient Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.6 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to patients through the Clinical Negligence Fund in Northern Ireland. QUB will provide indemnity for any negligent harm caused to patients by the design of the research protocol.

13.7 Data Access

All essential documentation i.e the Investigator Site file (ISF) and source data will be stored by sites. The TMF and associated trial data will be stored by the NICTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Following the publication of the primary and secondary study outcomes, there may be scope for the CI in the study to conduct additional analyses on the data collected. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission.

13.8 Record Retention

Archiving of essential documents will take place as outlined in the Sponsor Delegation Framework.

The site PI will be provided with an ISF by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for archiving of essential documents at local sites in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor on request. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

The TMF will be held by the CTU within the BHSCT and the essential documents that make up the TMF will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and as required by the BHSCT Sponsor.

13.9 Competing Interests

The research costs are funded by NIHR HTA. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC/TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC/TSC member reports a conflict of interest, advice will be sought from the Sponsor and the Funder.

14 DISSEMINATION/PUBLICATIONS

14.1 Publication Policy

The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Template for Intervention Description and Replication (TIDieR) checklist and guide (26, 33).

We plan to publish our trial protocol and statistical analysis plan to ensure transparency in our methodology. The study findings will be presented at national and international meetings with abstracts on-line. Presentation at these meetings will ensure that results and any implications quickly reach all of the UK intensive care community. This will be facilitated by our investigator group which includes individuals in executive positions in the UK Intensive Care Society. In accordance with the open access policies proposed by the NIHR we aim to publish the clinical findings of the trial as well as a paper describing the cost-effectiveness in the NHS setting in high quality peer-reviewed open access (via Pubmed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists. A final report will also be published in the NIHR HTA journal.

We will actively promote the findings of the study to journal editors and critical care opinion leaders to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. Due to limited resources, it will be not be possible to provide each patient with a personal copy of the results of the trial. However upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. The most significant results will be communicated to the public through press releases. An on-going update of the trial will also be provided on the NICTU website.

14.2 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

14.3 Data Sharing Statement

The study will comply with the good practice principles for sharing individual participant data from publicly funded clinical trials (41) and data sharing will be undertaken in accordance with the required regulatory requirements. Requests for data sharing will be reviewed on an individual basis by the CI.

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16 APPENDICES

Appendix 1	P/F ratio reference table for inclusion criteria
Appendix 2	ARDSNet PEEP/FiO_2 table
Appendix 3	List of expected adverse events
Appendix 4	Sub Study: Evaluation of Mechanisms in REST

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

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

Appendix 2: PEEP/FiO2 table

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

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

Appendix 3: List of expected adverse events:

Access site contamination

Acute kidney injury

Air embolism

Arterial puncture with needle during insertion

Arteriovenous fistula

Battery empty or low

Bleeding at the insertion site

Blood loss (Excessive) due to disconnection of the return blood path

Blood pressure decrease

Brachial plexus injury

Bradycardia

Breach of device / environment barrier

Cardiac arrhythmias

Catheter and/or blood circuit occlusion

Catheter related blood stream infection or cellulitis at insertion area

CO_2 removal - excessive or insufficient

Chylothorax

Death

Device malfunction

Disseminated Intravascular Coagulation (DIC)

Endocarditis

Exit site necrosis

External leak in gas pathway

Extravasation

Failure of controller to provide sweep gas

Haemorrhage not related to insertion site bleeding

Haematoma

Haemothorax

Haemolysis

Heparin Induced Thrombocytopenia (HIT)

Hepatic dysfunction

Hydrothorax

Hypothermia (primarily through extracorporeal circulation)

In-flow or out-flow blood path disconnected during use

Interference between the Hemolung catheter and other indwelling devices

Intolerance reaction to catheter or blood circuit

Kink in tubing

Laceration or perforation of vessels or viscus

Loss of AC power.

Low power (brownout)

Myocardial infarction or coronary insufficiency

Pericardial fluid collection, no cardiac tamponade

Pericardial fluid collection, with cardiac tamponade

Pleural effusion

Pneumomediastinum

Pneumothorax

Pulmonary embolism

Right heart failure

Shock

Stroke (Haemorrhagic/Thrombotic) or Transient Ischaemic Attack

Subcutaneous emphysema

Severe thrombocytopenia, non-HIT related

Subcutaneous emphysema

Tachycardia

Thoracic duct Injury

Thromboembolism, arterial non-CNS

Thromboembolism, venous event or vascular obstruction of Hemolung Catheter

Transposed connection of blood tubing

Ventricular thrombosis

Appendix 4: Sub Study: Evaluation of Mechanisms in Rest

The pathophysiological processes involved in ventilator-induced lung injury (VILI) are poorly understood. However, the REST trial offers a unique opportunity to develop our understanding of the mechanisms of VILI.

Aims

Between conventional mechanical ventilation, and lower tidal volume mechanical ventilation with the assistance of vv-ECCO$_2$R, we aim to investigate if there is a reduction in established pulmonary and systemic biomarkers implicated in the development of VILI. In addition, we will aim to identify novel biomarkers implicated in the development of VILI.

Population

Patients at selected sites recruited to the REST trial.

Additional trial procedures

The Principal Investigator (or designee) takes responsibility to ensure that written informed consent / advice is obtained for each participant prior to entry into this sub-study.

The process for agreement to participate in this sub-study will follow the same pathway outlined in the REST trial (see section 8.6.2 – 8.6.3 in the REST protocol). A separate covering statement, information sheet and personal consultee declaration will be provided for this sub-study.

Investigations

The additional investigations in this study are:

1. Blood sampling at baseline (i.e. before initiation of vv-ECCO2R), days 3 and 7.
2. Bronchoscopy, with bronchoalveolar lavage (BAL), at baseline and day 3.
3. Urine sampling at baseline, days 3, and 7.

Blood and urine sampling will be collected by trained study staff and processed according to standardised procedures (1,2). An additional blood sample (40ml) may be taken at baseline for monocyte or neutrophil isolation.

Bronchoscopy and BAL will be undertaken where possible, and processed as previously described (2,3). In keeping with standard recommendations, patients who are receiving more than 80% inspired oxygen or have a high positive end expiratory pressure (i.e. >10cm H2O) will not undergo bronchoscopy and BAL. In addition, if the ICU consultant has any concerns regarding safety the procedure will not be undertaken.

Participants will be closely monitored during and after bronchoscopy and BAL. Participants will receive sedation and analgesia (to prevent discomfort) as part of standard care. Bronchoscopy and BAL can be associated with transient oxygen desaturation. Patients will be pre-oxygenated. Predefined stopping criteria are established and if oxygen saturation, as measured by pulse oximetry, falls to <92% both bronchoscopy and BAL will be stopped. A sample will be sent for microbiological analysis.

All samples will be labelled with the patient's unique Subject Number, and will be stored at -80°C after processing until analysis. Samples will be stored beyond study completion in Queen's University Belfast. As new scientific data become available we will be able to use this resource of stored sample to investigate if this new data is relevant to ARDS pending additional ethical approval.

Exploratory Analyses

The following analyses are planned:

To assess systemic inflammatory responses, we will measure plasma and serum inflammatory response biomarkers which may include but are not limited to measurement of plasma CRP, cytokines (including but not limited to TNFα, IL1β, IL6, IL8), lipocalins, proteases and antiproteases, adhesion and activation molecule expression (including but not limited to sICAM1), NETs, coagulation factors (including but not limited to thrombin-antithrombin complex, tissue factor, protein C, thrombomodulin and plasminogen activator inhibitor1), and RAGE ligands will be undertaken, Specific cellular populations within the blood (using but not limited to cytospins and flow cytometry) and identification of transcriptome changes within these cell populations will be carried out.

Pulmonary inflammatory responses will be assessed via BAL biomarkers which may include but are not limited to the measurement of cytokines (including but not limited to TNFα, IL1β, IL6, IL8), proteases and antiproteases, coagulation factors (including but not limited to thrombin-antithrombin complex, tissue factor, protein C, thrombomodulin and plasminogen activator inhibitor1), and RAGE ligands will be undertaken. Identification of specific cellular populations within the BAL (using but not limited to cytospins, flow cytometry, ELISpot assays, in vitro cell expansion) will also be undertaken. Intracellular signalling activity in the alveolar space which may include but not limited to the measurement of BAL total and phosphorylated p38, ERK and JNK MAPKs and STAT -1/-3 from leucocyte extracts will be measured. Activated and total IκBα and β will be measured in cytoplasmic extracts and NFκβ and AP-1 in nuclear extracts.

Pulmonary and systemic epithelial and endothelial function and injury will be investigated by testing plasma, serum and BAL biomarkers which may include but are not be limited to measurement of RAGE, Ang I/II, SP-D, vWF, PCP3 as well as total protein, plasma albumin, α2-macroglobulin, and protein permeability (albumin:α2-macroglobulin ratio) will be undertaken. Urinary albumin/creatinine ratio will also be measured.

Lipid inflammatory mediators will be assessed through the analysis of BAL, serum, plasma and urine biomarkers which may include but not be limited to the measurement of thromboxane B2, prostaglandin E metabolite and 15-epi-lipoxin A4.

Samples from subjects will also be tested on primary cultures of fresh human neutrophils, monocytes and macrophages as well as mesenchymal stromal cells to determine surrogate markers of inflammation which may include but not be limited to the measurement of activation (shape change, CD11b surface expression, superoxide release), adhesion and transmigration, cytokine release and MMP production, rate of apoptosis and their ability to phagocytose.

Alveolar macrophages will be isolated from BAL to study the effects of the two ventilation strategies on alveolar macrophage function, which may include but not be limited to the measurement of inflammatory mediator release and apoptosis as well as response to anti-protease peptides in vitro. Alveolar macrophages will be co-cultured with human mesenchymal stromal cells in the presence of BAL fluid from the same patient to determine the effect on their functional properties (cytokine release, phagocytosis, polarization markers expression).

Monocytes or neutrophils will be isolated from blood at baseline. Cells will be stimulated (as monocytes) or matured for 5-7 days to produce monocyte-derived macrophages (MDMs). Cells (monocytes or MDMs) will be stimulated with LPS or other inflammatory stimuli to identify mechanisms modulating inflammatory responses in these cells during AHRF.

SAMPLE SIZE

The outcome in this sub-study is plasma C-reactive protein (CRP) at day 3. Previous clinical trials have shown a 40 – 60% reduction in systemic biomarkers of inflammation in patients receiving lower tidal volume ventilation compared to higher volume ventilator strategies (4,5). Based on a mean day 3 CRP of 135 (±100) (unpublished data), we will require 24 patients per group to detect a 60% reduction (β error 0.8, α error 0.05). To allow for the possibility of withdrawn consent after patients regain capacity, we plan to recruit at least 26 patients per group, totalling at least 52.

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