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A new way of treating patients with respiratory failure

Submission date 20/01/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 14/04/2016	**Overall study status** Completed	
Last Edited 18/08/2025	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims

The researchers running this study want to test a new way of treating respiratory failure. When people are very ill their lungs often stop working. This is called respiratory failure. As a result, breathing becomes difficult and they need to be treated in an intensive care unit (ICU) where they will be connected to a machine to help their breathing. This is called mechanical ventilation. Respiratory failure is common in the UK; about 100,000 people each year need treatment with mechanical ventilation. Almost half of these patients die. Although there is evidence that mechanical ventilation does save lives, it can be linked with damage to the lungs. A mechanical ventilator acts like bellows as air is forced into the lungs under pressure. If the pressure needed to help the patient breathe is too high this can cause lung damage. New devices are now available to help patients breathe. These devices help remove carbon dioxide from the patient's blood, which is one of the main functions of the lungs. This may allow more gentle mechanical ventilation. This more gentle ventilation may cause less harm to the lungs and improve the outcome of patients with respiratory failure. These new devices involve a tube called a catheter being placed in a large blood vessel called a vein. Blood passes from the patient through the device where it is "washed" to remove carbon dioxide before it is returned to the patient. This is called extracorporeal carbon dioxide removal. Kidney dialysis uses very similar equipment. Kidney dialysis is common for patients admitted to intensive care units and doctors are used to putting this type of catheter into patients on the ICU. These new devices may help doctors and nurses care for patients with respiratory failure, but there is not enough information about the devices to help them decide whether they are helpful or not. This study investigates whether they work or not.

Who can participate?

Patients aged at least 16 with respiratory failure and have been admitted to an intensive care unit (ICU).

What does the study involve?

Patients are randomly allocated to one of two groups. Those in group 1 are given the best level of care that is advised by current NHS guidelines. Those in group 2 also receive the best level of care but are, in addition, also treated with the device to remove carbon dioxide from their blood to allow the pressure in their lungs to be reduced. The treatment a patient receives is decided at

random by a computer programme and at the end of the study researchers will know whether this new device reduces death from respiratory failure and look at the long-term survival and quality of life of the patients in the study. The cost of using the new device compared to usual care is also investigated.

What are the possible benefits and risks of participating?
Taking part in this study may have contributed to improved treatment of patients with acute respiratory failure in the future. ECCO2R is a procedure that is used in the UK in patients who have respiratory failure. A previous study found ECCO2R was well tolerated and associated with few side effects (about one in every 40 patients); however all procedures have potential side effects. Side effects of ECCO2R include complications with catheter placement such as blood vessel damage, dislodgement, infection and an increased risk of bleeding. Catheter insertion is similar to other tubes that are placed in the neck or groin veins during any ICU admission with respiratory failure and carry the same level of risk. To minimise such risks, the catheter is inserted with the help of ultrasound. Ultrasound is a medical test that uses soundwaves to capture live images from the inside of the body; this helped the doctor to directly see the blood vessel and ensure a more accurate insertion of the catheter. The potential complications whilst ECCO2R is running are uncommon and include clot formation within the device or the blood vessel (reduced by anticoagulation) or air entrainment into the device (reduced by safety mechanisms within the device). Bleeding can also occur in any patient placed on blood thinning agents (anticoagulation) and although uncommon (less than one in every 50 patients) can be significant, requiring blood transfusion and can potentially lead to serious bleeding. To minimise this risk of bleeding we regularly measured the effect of blood thinning agents on the ability of the blood to clot. All participants in the trial are monitored to ensure that any side effects are promptly picked up. ECCO2R would be stopped if they occur.

Where is the study run from?
The study is run in many ICUs in NHS hospitals in the UK.

When is the study starting and how long is it expected to run for?
June 2016 to April 2022

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Miss Colette Jackson
REST@nictu.hscni.net

Contact information

Type(s)
Public

Contact name
Miss Colette Jackson

ORCID ID
https://orcid.org/0000-0001-7814-0749

Contact details

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Additional identifiers

EudraCT/CTIS number
2015-005280-17

IRAS number

ClinicalTrials.gov number
NCT02654327

Secondary identifying numbers
15084DMcA-AS

Study information

Scientific Title
PRotective vEntilation with veno-venouS lung assisT in respiratory failure

Acronym
The REST Trial

Study objectives
In adult patients who require invasive mechanical ventilation for acute hypoxaemic respiratory failure, VV-ECCO2R and lower tidal volume ventilation results in reduced mortality.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Current ethics approval as of 23/05/2017:
1. South Berkshire REC England, Wales and Northern Ireland, 14/03/2016, ref: 16/SC/0089
2. Scotland A REC, Scotland, 23/03/2016, ref:16/SS/0048

Previous ethics approval:
Office of Research Ethics Committees Northern Ireland, 14/03/2016 (England and Wales)

Study design
Randomised, allocation concealed, controlled, open, pragmatic clinical and cost effectiveness trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Acute hypoxaemic respiratory failure

Interventions
Current interventions as of 05/03/2019:
Intervention treatment will last for up to 7 days, patient follow up will be for 12 months.

INTERVENTION ARM: A dual lumen catheter will be inserted into a central vein and veno-venous extracorpoeal carbon dioxide removal (vv-ECCO2R) initiated within 8-24 hours of consent. The pump blood flow rate and gas flow through the vv-ECCO2R device will be set up according to study manual. Thereafter tidal volumes on mechanical will be gradually decreased to approximately 3ml/kg predicted body weight, maintaining arterial pH of greater than 7.2 and plateau pressure less than or equal to 25cm H2O. A heparin infusion is used as anticoagulation to prevent circuit clotting. vv-ECCO2R will be considered for weaning after a minimum of 48 hours when weaning criteria are achieved.

CONTROL ARM: Standard management of acute hypoxamic respiratory failure with mechanical ventilation set according to the ARDSNetwork trial aiming for tidal volumes less than 6ml/kg predicted body weight and plateau pressure less than or equal to 30cm H2O.

Previous interventions:
Intervention treatment will last for up to 7 days, patient follow up will be for 12 months.

INTERVENTION ARM: A dual lumen catheter will be inserted into a central vein and veno-venous extracorpoeal carbon dioxide removal (vv-ECCO2R) initiated as soon as possible and no later than 8 hours after randomisation. The pump blood flow rate and gas flow through the vv-ECCO2R device will be set up according to study manual. Thereafter tidal volumes on mechanical will be gradually decreased to less than or equal to 3ml/kg predicted body weight maintaining arterial pH of greater than 7.2 and plateau pressure less than or equal to 25cm H2O. A heparin infusion is used as anticoagulation to prevent circuit clotting. vv-ECCO2R will be considered for weaning after a minimum of 48 hours when weaning criteria are achieved.

CONTROL ARM: Standard management of acute hypoxamic respiratory failure with mechanical ventilation set according to the ARDSNetwork trial aiming for tidal volumes less than 6ml/kg predicted body weight and plateau pressure less than or equal to 30cm H2O.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Not provided at time of registration

Primary outcome measure
Mortality at 90 days after randomisation

Secondary outcome measures
Current secondary outcome measures as of 23/05/2017:
1. Tidal volume (ml/kg PBW) at day 1 and day 3 after randomisation (updated 05/03/2019: 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. Saint 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

Previous secondary outcome measures:
1. Tidal volume (ml/kg PBW) at day 1 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. Saint George's Respiratory Questionnaire (SGRQ) at 1 year and need for home oxygen at 6 months and 1 year after randomisation

Added 05/03/2019:
Exploratory outcomes:
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)

Overall study start date
01/03/2016

Completion date
30/04/2022

Eligibility

Key inclusion criteria
1. Invasive mechanical ventilation using PEEP ≥ 5cmH2O*
2. Acute and potentially reversible cause of acute respiratory failure as determined by the treating physician
3. Within 48 hours of the onset of hypoxaemia as defined by PaO2/FiO2 ≤ 20kPa**

*Recommended on low tidal volume ventilation ≤ 6 ml/kg PBW
**Requires two ABG with a PaO2/FiO2 ≤ 20kPa separated by at least 6 hours. 48 hour duration begins at the time of 2nd ABG demonstrating PaO2/FiO2 ratio ≤ 20kPa. Added 05/03/2019: Site will then have a further 8 – 24 hours to randomise and administer the intervention. Added 23/05 /2017: The onset of hypoxaemia is from time of intubation and invasive ventilation.

(ABGs with PaO2/FiO2 ≥ 20kPa are permitted between the two trial inclusion ABGs).

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
1120

Total final enrolment
412

Key exclusion criteria
Current exclusion criteria as of 23/05/2017:
1. Age <16 years old
2. Intubated and mechanically ventilated via an endotracheal or tracheostomy tube ≥ 7 days (168 hours) up to the time of randomisation
3. Ability to maintain Vt to ≤ 3ml/kg PBW while maintaining pH ≥ 7.2 as determined by the treating physician
4. Receiving, or decision to commence, ECMO in the next 24 hours.
5. Mechanical ventilation using HFOV or APRV
6. Untreated pulmonary embolism, pleural effusion or pneumothorax as the primary cause of acute respiratory failure.
7. Acute respiratory failure fully explained by left ventricular failure or fluid overload (May be determined by clinical assessment or echocardiography/cardiac output monitoring).
8. Left ventricular failure requiring mechanical support
9. Contra-indication to limited systemic anticoagulation with heparin
10. Unable to obtain vascular access to a central vein (internal jugular or femoral vein)
11. Inferior vena cava filter (if using femoral vein catheter)
12. Consent declined
13. Treatment withdrawal imminent within 24 hours
14. Patients not expected to survive 90 days on basis of premorbid health status
15. DNAR (Do Not Attempt Resuscitation) order in place (added 05/03/2019: excluding advance directives)

16. Severe chronic respiratory disease requiring domiciliary ventilation (except for sleep disordered breathing)
17. Severe chronic liver disease (Child Pugh >11)
18. Platelet count < 40,000 mm3 (added 05/03/2019: prior to catheter insertion)
19. Previously enrolled in the REST trial
20. Prisoners

Previous exclusion criteria:
1. Age <16 years old
2. Intubated and mechanically ventilated via an endotracheal or tracheostomy tube ≥ 7 days (168 hours) up to the time of randomisation
3. Ability to maintain Vt to ≤ 3ml/kg PBW while maintaining pH ≥ 7.2 as determined by the treating physician
4. Receiving, or decision to commence, ECMO in the next 24 hours.
5. Mechanical ventilation using HFOV or APRV
6. Untreated pulmonary embolism, pleural effusion or pneumothorax as the primary cause of acute respiratory failure.
7. Acute respiratory failure fully explained by left ventricular failure or fluid overload (May be determined by clinical assessment or echocardiography/cardiac output monitoring).
8. Left ventricular failure requiring mechanical support
9. Contra-indication to limited systemic anticoagulation with heparin
10. Unable to obtain vascular access to a central vein (internal jugular or femoral vein)
11. Inferior vena cava filter (if using femoral vein catheter)
12. Consent declined
13. Treatment withdrawal imminent within 24 hours
14. Patients not expected to survive 6 months on basis of premorbid health status
15. DNAR (Do Not Attempt Resuscitation) order in place
16. Severe chronic respiratory disease requiring domiciliary ventilation (except for sleep disordered breathing)
17. Severe chronic liver disease (Child Pugh >11)
18. Platelet count < 40,000 mm3
19. Previously enrolled in the REST trial

Date of first enrolment
01/06/2016

Date of final enrolment
11/02/2020

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Royal Hospitals
Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
St Thomas' Hospital
London
United Kingdom
SE1 7EH

Study participating centre
Kings College Hospital
London
United Kingdom
SE5 9RS

Study participating centre
Manchester Royal Infirmary
Manchester
United Kingdom
M13 9WL

Study participating centre
St James Hospital, Leeds
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Hammersmith Hospital
London
United Kingdom
W12 0HS

Study participating centre
Charing Cross Hospital
London
United Kingdom
W6 8RF

Study participating centre
Royal Infirmary of Edinburgh
Edinburgh
United Kingdom
EH16 4SB

Study participating centre
Birmingham Heartlands Hospital & Good Hope
Birmingham
United Kingdom
B9 5SS

Study participating centre
Wythenshawe Hospital
Manchester
United Kingdom
M23 9LT

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TH

Study participating centre
Royal Liverpool University Hospital
Liverpool
United Kingdom
L7 8XP

Study participating centre

Royal Free Hospital
London
United Kingdom
NW3 2QG

Study participating centre
University Hospital of Wales
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Addenbrookes Hospital
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Royal Victoria Infirmary
Newcastle
United Kingdom
NE1 4LP

Study participating centre
Papworth Hospital
Cambrideshire
United Kingdom
CB23 3BE

Study participating centre
Royal Blackburn Hospital
Blackburn
United Kingdom
BB2 3HH

Study participating centre

John Radcliffe Hospital
Oxford
United Kingdom
OX3 9DU

Study participating centre
Royal Berkshire Hospital
Reading
United Kingdom
RG1 5AN

Study participating centre
Sandwell General Hospital
West Bromwich
United Kingdom
B71 4HJ

Study participating centre
Poole Hospital
Poole
United Kingdom
BH15 2JB

Study participating centre
Royal Cornwall Hospital
Cornwall
United Kingdom
TR1 3LJ

Study participating centre
Worcester Royal Hospital
Worcester
United Kingdom
WR5 1DD

Study participating centre

New Cross Hospital
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
St Georges Hospital
Tooting
United Kingdom
SW17 0QT

Study participating centre
Altnagelvin Hospital
Derry
United Kingdom
BT47 6SB

Study participating centre
Royal Stoke Hospitals
Stoke
United Kingdom
ST4 6QG

Study participating centre
Royal Infirmary
Glasgow
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Study participating centre
Norfolk & Norwich University Hospital
Norwich
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NR4 7UY

Study participating centre

Pinderfields Hospital
Wakefield
United Kingdom
WF1 4DG

Study participating centre
Aintree University Hospital
Liverpool
United Kingdom
L9 7AL

Study participating centre
Antrim Area Hospital
Antrim
United Kingdom
BT41 2RL

Study participating centre
Royal London Hospital
London
United Kingdom
E1 1BB

Study participating centre
Queen Elizabeth Hospital
Glasgow
United Kingdom
G51 4TF

Study participating centre
Chelsea & Westminster Hospital
London
United Kingdom
SW10 9NH

Study participating centre
Derriford Hospital
Derriford Rd
Plymouth

United Kingdom
PL6 8DH

Study participating centre
Musgrove Park Hospital
Stockmans Ln
Belfast
United Kingdom
BT9 7JB

Study participating centre
Northwick Park Hospital
Watford Rd
Harrow
United Kingdom
HA1 3UJ

Study participating centre
Queen Alexandra Hospital
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Royal Brompton Hospital
Sydney St
Chelsea
London
United Kingdom
SW3 6NP

Study participating centre
Royal Gwent Hospital
Cardiff Rd
Newport
United Kingdom
NP20 2UB

Study participating centre

Royal Oldham Hospital
Rochdale Rd
Oldham
United Kingdom
OL1 2JH

Study participating centre
University College Hospital
235 Euston Rd
Fitzrovia
London
United Kingdom
NW1 2BU

Study participating centre
York Teaching Hospital
Wigginton Rd
York
United Kingdom
YO31 8HE

Sponsor information

Organisation
Belfast Health & Social Care Trust

Sponsor details
Research Office, 2nd Floor King Edward Building
Royal Hospitals, Grosvenor Road,
Belfast
Northern Ireland
United Kingdom
BT12 6BA

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Not defined

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
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.

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from rest@nictu.hscni.net or call +44 28 9615 1447 and ask for a member of the REST team

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			15/04/2016	No	Yes
Results article		21/09/2021	20/05/2022	Yes	No
Protocol file	version 6.0	15/04/2021	23/08/2022	No	No
HRA research summary			28/06/2023	No	No
HRA research summary			28/06/2023	No	No
Other publications	cost-utility analysis	23/08/2023	17/10/2023	Yes	No