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pRotective vEntilation with veno-venouS lung assisT in respiratory failure. The REST Trial

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This issue

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Synopsis

Extracorporeal carbon dioxide removal for the treatment of acute hypoxaemic respiratory failure: the REST RCT

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Abstract

Background: In patients who require mechanical ventilation for acute hypoxaemic respiratory failure, further reduction in tidal volumes, compared with conventional low tidal volume ventilation, may improve outcomes.
Objective: To determine whether using extracorporeal carbon dioxide removal improves outcomes in patients with acute hypoxaemic respiratory failure and is cost-effective.
Design: A multicentre, randomised, allocation-concealed, open-label, pragmatic clinical trial.
Setting: Fifty-one intensive care units across the United Kingdom.
Participants: Four hundred and twelve adult patients receiving mechanical ventilation for acute hypoxaemic respiratory failure, of a planned sample size of 1120.
Interventions: Lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal for at least 48 hours (n = 202) or standard care with conventional low tidal volume ventilation (n = 210).
Main outcome measures: All-cause mortality 90 days. Secondary outcomes included ventilator-free days; adverse events; extracorporeal membrane oxygenation use; long-term mortality; health-related quality of life; health service costs; long-term respiratory morbidity.
Results: The trial was stopped early because of futility and feasibility. The 90-day mortality rate was 41.5% in the extracorporeal carbon dioxide removal group versus 39.5% in the standard care group (risk ratio 1.05, 95% confidence interval 0.83 to 1.33; difference 2.0%, 95% confidence interval − 7.6% to 11.5%; p = 0.68). There were significantly fewer mean ventilator-free days in the extracorporeal carbon dioxide removal group compared with the standard care group (7.1, 95% confidence interval 5.9 to 8.3) versus (9.2, 95% confidence interval 7.9 to 10.4) days; mean difference, −2.1 (95% confidence interval −3.8 to −0.3; p = 0.02). Serious adverse events were reported for 62 patients (31%) in extracorporeal carbon dioxide removal group and 18 (9%) in the standard care group, including intracranial haemorrhage in 9 patients (4.5%) versus 0 (0%) and bleeding at other sites in 6 (3.0%) versus 1 (0.5%) in the extracorporeal carbon dioxide removal group versus the control group. Two-year mortality data were available for 95% of patients. There was no difference in the time to death between groups (hazard ratio 1.08, 95% confidence interval 0.81 to 1.44; log-rank test p = 0.61). There was no difference in long-term outcomes between groups. There was no difference in quality-adjusted life-years at 12 months (mean difference −0.01, 95% confidence interval −0.06 to 0.05). Total 12-month costs were statistically significantly higher in the extracorporeal carbon dioxide removal group (mean difference £7668.76, 95% confidence interval £159.75 to £15,177.77). Secondary analyses indicated there may be heterogeneity of treatment effect based on physiological characteristics of the patients. A systematic review supported these findings.

This synopsis should be referenced as follows:
McNamee JJ, Agus A, Boyle AJ, Jackson C, McDowell C, Haglund J, McAuley DF. Extracorporeal carbon dioxide removal for the treatment of acute hypoxaemic respiratory failure: the REST RCT. *Health Technol Assess* 2025;**29**(33):1–16. https://doi.org/10.3310/GJDM0320

Limitations: Only 6% of screened patients were included in the study; most sites were naive to the intervention before the study commenced; other aspects of care were not standardised in each group, because this was a pragmatic trial; the trial may have been underpowered to detect a clinically important difference, because the trial was stopped early; blinding to the clinicians or patients was not possible.
Conclusions: There were no short- or long-term benefits found, and the device was associated with higher cost and potentially significant complications. We would advise against using this device in addition to standard care for the treatment of patients with hypoxaemic respiratory failure, outside of future clinical trials.
Future work: Future studies could further explore whether different patient populations receiving a larger 'dose' of from extracorporeal carbon dioxide removal might benefit, use core outcome sets and collect broader long-term outcomes and consider measuring patients' health-related quality of life at the soonest opportunity after regaining capacity.
Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 13/143/02.
A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GJDM0320.

Introduction

This report summarises the work undertaken to assess the clinical and cost-effectiveness of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal ($ECCO_2R$) compared to ventilation alone in patients with acute hypoxaemic respiratory failure (AHRF). The trial was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme, award number 13/143/02, following a commissioned call. The trial was prospectively registered on ClinicalTrials.gov (NCT02654327) and International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN31262122).

In the UK, over 100,000 patients each year require mechanical ventilation in the intensive care unit (ICU), of whom over 15,000 patients have AHRF. AHRF is a major cause of morbidity and mortality and has significant resource implications in terms of ICU and hospital stay. Survivors often have long-term physical and cognitive impairment requiring support in the community after hospital discharge.[1–3] The high incidence, mortality, long-term consequences and high economic costs mean that AHRF is an extremely important problem. Mechanical ventilators delivering high pressures and volumes can cause regional overdistension in the injured lung, resulting in further inflammation and damage. The release of inflammatory mediators from the damaged lung causes systemic inflammation, leading to multiorgan failure and death.[4] One of the few interventions shown to reduce mortality in patients with ARHF is ventilation with a lung-protective strategy aiming for a tidal volume of 6 ml/kg predicted body weight and a plateau pressure ≤ 30 cm H_2O in patients.[5] However, even when using lung-protective invasive mechanical ventilation, damage can still occur. Reducing tidal volumes further may result in respiratory acidosis, which can cause further adverse effects, such as pulmonary hypertension and altered cardiac function.[6] Extracorporeal gas exchange, including $ECCO_2R$, can facilitate mechanical ventilation with even lower tidal volumes, because it supports the removal of carbon dioxide (CO_2) that accumulates in this setting.[7,8] The feasibility of $ECCO_2R$ in patients with AHRF has recently been demonstrated.[9]

The primary objective of the pRotective vEntilation with veno-venouS lung assisT in respiratory failure (REST) trial was to determine whether lower tidal volume ventilation facilitated by $ECCO_2R$ compared with standard care in patients with AHRF decreases mortality 90 days after randomisation.

A publication plan was agreed with NIHR which set out how we intended to report the funded work in the threaded publication model. The publications are presented in *Table 1* along with DOI links. A brief summary is provided for each of the papers, as they are already in the public domain. We also provide a substantial narrative addressing the considerable trial management resource that was required to deliver this multicentre trial of a medical device.

Protocol

Full details of the study, including the objectives, data collection methods and the planned analyses, were published as a protocol.[10] The statistical analysis plan was made publicly available here: https://nictu.hscni.net/download/74/rest-study/8232/rest-sap-v1-0-final-161219.pdf.

Primary outcome and short-term secondary outcomes

The short-term trial results were published in the *Journal of the American Medical Association*.[11] In total, 412 adult patients receiving mechanical ventilation for

TABLE 1 pRotective vEntilation with veno-venouS lung assisT in respiratory failure publication plan

Project element	Reference
Protocol	McNamee JJ, Gillies MA, Barrett NA, Agus AM, Beale R, Bentley A, *et al.* pRotective vEntilation with veno-venouS lung assisT in respiratory failure: a protocol for a multicentre randomised controlled trial of extracorporeal carbon dioxide removal in patients with acute hypoxaemic respiratory failure. *J Intensive Care Soc* 2017;**18**:159–69. https://doi.org/10.1177/1751143716681035[10]
Primary outcome and other short-term secondary outcomes	McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, *et al.* Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs. standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA*. 2021;**326**:1013–23. https://doi.org/10.1001/jama.2021.13374. [Erratum published in *JAMA*. 2022;327:86.][11]
Long-term outcomes	Boyle AJ, McDowell C, Agus A, Logan D, Stewart JD, Jackson C, *et al.* Acute hypoxaemic respiratory failure after treatment with lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal: long-term outcomes from the REST randomised trial. *Thorax* 2023;**78**:767–74. https://doi.org/10.1136/thorax-2022-218874[12]
Health economic evaluation	Agus A, McNamee JJ, Jackson C and McAuley DF. Extracorporeal carbon dioxide removal compared to ventilation alone in patients with acute hypoxaemic respiratory failure: cost–utility analysis of the REST RCT [published online ahead of print August 23 2023]. *Health Technol Assess* 2023. https://doi.org/10.3310/FCDQ8036[13]
Evidence synthesis study	Millar JE, Boyle AJ, Drake TM, Adams CE, Glass AW, Blackwood B. *et al.* Extracorporeal carbon dioxide removal in acute hypoxaemic respiratory failure: a systematic review, Bayesian meta-analysis and trial sequential analysis. *Eur Respir Rev* 2022;**31**:220030. https://doi.org/10.1183/16000617.0030-2022[14]
Secondary Bayesian analysis study	Dianti J, McNamee JJ, Slutsky AS, Fan E, Ferguson ND, McAuley DF, *et al.* Determinants of effect of extracorporeal CO_2 removal in hypoxemic respiratory failure. *NEJM Evid*. 2023;**2**. https://doi.org/10.1056/EVIDoa2200295[15]
Exploratory post hoc analysis study	Goligher EC, McNamee JJ, Dianti J, Fan E, Ferguson ND, Slutsky AS, *et al.* Heterogeneous treatment effects of extracorporeal CO_2 removal in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2023;**208**:739–42. https://doi.org/10.1164/rccm.202304-0689LE[16]
Cardiac function study	McGuigan PJ, Bowcock EM, Barrett NA, Blackwood B, Boyle AJ, Cadamy AJ, *et al.* The effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal compared with conventional lung protective ventilation on cardiac function. *Crit Care Explor* 2024;**6**:e1028. https://doi.org/10.1097/CCE.0000000000001028. PMID: 38213419; PMCID: PMC10783412[16]
Trial delivery	Included in synopsis

This synopsis should be referenced as follows: McNamee JJ, Agus A, Boyle AJ, Jackson C, McDowell C, Haglund J, McAuley DF. Extracorporeal carbon dioxide removal for the treatment of acute hypoxaemic respiratory failure: the REST RCT. *Health Technol Assess* 2025;**29**(33):1–16. https://doi.org/10.3310/GJDM0320

AHRF were randomised to receive either lower tidal volume ventilation facilitated by $ECCO_2R$ for at least 48 hours (n = 202) or standard care with conventional low tidal volume ventilation (n = 210). Following recommendations from the Data Monitoring and Ethics Committee, the trial was stopped early because of futility and feasibility therefore did not achieve the planned sample size of 1120. There was no significant difference in the primary outcome of all-cause 90-day mortality {41.5% in the $ECCO_2R$ group vs. 39.5% in the standard care group; difference 2.0% [95% confidence interval (CI) −7.6% to 11.5%]; p = 0.68}. There were significantly fewer mean ventilator-free days in the $ECCO_2R$ group compared with the standard care group; mean difference, −2.1 (95% CI −3.8 to −0.3; p = 0.02). Serious adverse events (SAEs) were reported for 62 patients (31%) in $ECCO_2R$ group and 18 (9%) in the standard care group. We concluded that in patients with AHRF, the use of $ECCO_2R$ to facilitate lower tidal volume mechanical ventilation, compared with conventional low tidal volume mechanical ventilation, did not significantly reduce 90-day mortality. However, the study may have been underpowered to detect a clinically important difference.

Long-term outcomes

A pre-specified analysis of the longer-term outcomes collected in the REST trial was published in *Thorax*.[12] Two-year mortality data were available for 391/412 (95%), and there was no difference in the time to death between groups [hazard ratio 1.08 (95% CI 0.81 to 1.44); log-rank test p = 0.61]. One hundred and sixty-one out of 227 (71%) survivors at 1 year provided at least one questionnaire response. There was no difference in respiratory function, post-traumatic stress disorder, cognitive dysfunction or health-related quality of life (HRQoL) between patients in the between groups. We concluded that lower tidal volume ventilation facilitated by $ECCO_2R$ in patients with AHRF did not affect long-term mortality, long-term respiratory function, post-traumatic stress disorder, cognitive dysfunction or HRQoL.

Health economic evaluation

The cost-effectiveness of $ECCO_2R$ compared to standard ventilation in patients with AHRF was assessed at 12 months post randomisation via a cost–utility analysis embedded within the REST trial. The results were published in the NIHR Journals Library.[13] Standard care dominated $ECCO_2R$, and there was 0% probability of $ECCO_2R$ being cost-effective compared to ventilation alone in patients with AHRF for all thresholds of willingness to pay per quality-adjusted life-year considered (£0–50,000).

Evidence synthesis study

Given the uncertainty surrounding the role of $ECCO_2R$ in AHRF following the early closure of the REST trial to futility, a systematic review, Bayesian meta-analysis and trial sequential analysis were performed. The results were published in the *European Respiratory Review*.[14] Twenty-one studies met the inclusion criteria: three RCTs, enrolling 531 patients, and 18 observational studies. We concluded that the use of $ECCO_2R$ in patients with AHRF is not associated with improvements in clinical outcomes. Furthermore, it is likely that further trials of $ECCO_2R$ aiming to achieve an absolute risk reduction in mortality of ≥ 10% are futile.

Planned secondary Bayesian analysis study

A secondary analysis of the REST trial data was planned prior to the availability of the trial results to test whether the effect of $ECCO_2R$ on mortality varied according to different moderators. The results were published in the *New England Journal of Medicine Evidence*.[15] Bayesian logistic regression was used to estimate the posterior probability of effect moderation by ventilatory ratio, respiratory system elastance and severity of hypoxaemia on 90-day mortality. We concluded that ventilator ratio has a highly credible influence on the effect of $ECCO_2R$ on mortality and that $ECCO_2R$ reduce mortality in patients with high ventilatory ratio.

Exploratory post hoc analysis study

A post hoc exploratory analysis was carried out to explore heterogeneous treatment effects of $ECCO_2R$. The results were published as a letter in the *American Journal of Respiratory and Critical Care Medicine*.[15] The study set out to identify subsets of patients whose treatment effect differed substantially from the average treatment effect (i.e. benefit or harm). We concluded that the effect of $ECCO_2R$ on mortality varied widely in the REST trial. Despite the overall trial's negative results, the subset of patients with a higher predicted absolute risk reduction exhibited a high probability of mortality benefit with this intervention.

Cardiac function study

A planned exploratory analysis was conducted looking at the right heart function via tricuspid annular plane systolic excursion on echocardiography and the serum biomarker N-terminal pro-B-type natriuretic peptide (NT-pro-BNP).[16] Thirteen patients from the $ECCO_2R$ group were compared to 8 patients in standard care group on echocardiography and 36 patients on $ECCO_2R$, and 39 patients on standard care group were compared using serum NT-pro-BNP. We found no statistically significant difference in cardiac function between the two groups.

Discussion

Trial delivery challenges, strategies and lessons learnt

The delivery of a multicentre trial of a medical device in the critical care setting had many challenges. In this narrative piece, we first describe how the $ECCO_2R$ device was selected and how this informed the study protocol. We then describe how the trial management team at the Northern Ireland Clinical Trials Unit co-ordinated the delivery of protocol and device training to staff at 51 ICUs across the UK, and how they dealt with recruitment challenges and medical device issues.

Working with industry

The intervention arm of the trial required the insertion of a central venous access catheter and the use of an $ECCO_2R$ device. The protocol was always designed to ensure the generic application of this intervention which did not favour one device over another. This was to avoid suggestions of specific commercial promotion. At the time of the study conception and trial design, there were no published data which demonstrated major difference in performance characteristics of the available devices on the market. Each of the three companies that supply $ECCO_2R$ devices to the UK were evaluated using pre-defined criteria. These were:

1. user-friendly device: catheter and console
2. experience throughout the UK
3. support network for distribution and maintenance.

Co-applicants of our trial team had experience in using all three available devices currently available in UK. ALung Technologies, Inc. (Pittsburgh, PA, USA) met all of these pre-defined criteria and therefore we approached them first to negotiate supporting the trial. The company agreed to supply devices and consumables and provide training and support with no charge. Therefore, as they were our preferred device manufacturer, we elected to choose them for our trial. Preference was given to the company with the capability of a support and distribution network throughout the UK as this was a key requirement for trial delivery. If our preferred company failed to deliver on this, then we could move to the next favoured company, as the trial was designed to test the health technology of $ECCO_2R$, irrespective of the device used. The estimated costs for 40 sites (the initial target number) and the 560 patients randomised to receive $ECCO_2R$ over the course of the study was in the range of £4.8 million. This was a major saving, which would otherwise have had to be met by the NHS. The devices were to be provided without any conditions, and the trial team would have complete responsibility for protocol development, ownership of trial data, and no intellectual property would be assigned to the company. Legal negotiations established a contractor's collaboration agreement, whereby any intellectual property that could potentially arise following the study and the ownership of data would be the property of the funder.

Initial communication with the manufacturers ensured that the medical device in question had already been Conformité Européenne (CE) marked and was to be used within the scope of its CE mark. Medicines and Healthcare products Regulatory Agency (MHRA) authorisation was not required, as we were using the device within its intended use and indications for MHRA purposes. We were informed at that time that the device was validated for use up to 7 days and that time limit informed the subsequent study protocol. We were provided with the full list of known complications, and the manufactures were able to guarantee that they would provide intensive training and full technical support on the use of the device for the first few cases at each site. With regard to indemnity, the company accepted liability for any negligence in their part in relation to the manufacture of the equipment or any associated services (training, maintenance, etc.). This level of support was subsequently delivered to each site as the trial progressed.

Delivery of the training

A clinical training group was formed with the responsibility for the setup and training of all clinical and research staff at the recruiting sites. This group was made up of experts in trial management, study protocol, extracorporeal technology, research nursing staff and $ECCO_2R$ device support staff. All recruiting sites were provided with a comprehensive training package prior to being given the green light to open to recruitment. The training package covered the study protocol, study manual (document intended to give an overview of providing $ECCO_2R$ therapy and ventilation management as part of the REST trial) use of the MACRO clinical database and $ECCO_2R$ device training. To ensure maximum effectiveness, several formats were used to deliver the study-training package. These included:

- protocol and study manual presentations delivered by webinar
- flow charts on the identification and reporting of adverse events (AEs) and SAEs
- guidelines on the randomisation process and training requirements

- frequently asked questions (FAQs)
- online instructional videos and printed documentation on the use of the $ECCO_2R$ device
- onsite practical device training sessions delivered by the device provider and the research nurses
- access to an online study specific training platform.

Once the training package was delivered, all delegated staff members were then required to provide training logs documenting the specific training undertaken. This documentation was held centrally at the clinical trials unit (CTU) and tracked using a dedicated spreadsheet to ensure that all delegated staff had completed the full required package before taking on their delegated role as allocated by the principal investigator (PI).

As the study was being conducted in multiple UK sites, the decision was made to deliver the training presentations via webinar rather than onsite visits. There were several advantages to this approach: it allowed staff from several sites to attend the same training sessions, it allowed site staff to select a time slot that suited them best; it removed the administrative resource associated travel time and it removed travel costs. Overall, it accelerated the opening of sites for recruitment.

Site training package

In order to successfully deliver the site training package to over 51 sites, a high level of administrative resource was required to schedule and undertake this. The trial team responsible for setting up and delivering the training package consisted of five full-time staff: one trial manager, one trial co-ordinator, one administrator and two research nurses. The team worked together to successfully schedule and deliver training to the sites throughout the duration of the REST trial. Activities required for this task included:

- creating presentations for protocol and study manual training
- creating documentation and preparing study files (investigator site files/trial manuals/flow charts/guidelines and FAQs)
- arranging the couriering of these documents to sites
- liaising with sites to schedule and deliver training sessions
- provision of additional support to site staff to resolve any queries.

The site training package was broken down into three different training aspects:

Protocol – the trial manager or co-ordinator provided protocol training and covered protocol-specific areas, such as study objectives, inclusion/exclusion, consent, data collection, monitoring and AE reporting among others.

Study manual – the study manual training was provided initially by the clinical lead and then by the study research nurses when in post. The basis for this training was the device study manual. The areas covered included the equipment for $ECCO_2R$, setup and cannulation, starting/adjusting therapy, clinical care of patient on therapy, troubleshooting and weaning/ending therapy.

MACRO training – this training was provided by the study data manager who, prior to the session, provided remote MACRO training access to sites and then navigated them through the database clarifying the data being collected and demonstrating how to use the system. Sites would then be given the chance to ask questions and revisit sections if needed.

Lessons learnt from site training package

Site feedback was very positive, highlighting that the training was comprehensive and successful in preparing sites to undertake the study. Sites indicated that they felt that the training sessions met their needs and found the flexibility to attend any suitable timeslots very beneficial in ensuring that all site staff involved in the study were captured. The online delivery of the programme also brought positive benefits to the study overall in terms of resource use and costs as no travel time or finance was required to deliver the training, which resulted in an increase in available administrative resource and subsequent financial benefits for the study budget. The CTU did experience some technical issues with accessing webinar at some sites due to site information technology (IT) department restrictions; however, the trial team put an additional step in and undertook a webinar test in preparation for the sessions to ensure that any resulting technical issues could be addressed before the scheduled training. The trial team did feel that the online delivery did not offer the usual face-to-face contact that always helps to create a successful working relationship with sites in the early stages of a study. To mitigate this, the trial team held study meetings at ICU conferences in order to encourage working relationships with the site teams, which was a positive experience for all involved. Overall, the delivery of the online programme was a success, and as a result, future CTU studies will also now deliver their training online using video-conferencing software, which have become more prevalent in a post-COVID-19 environment to allow face-to-face interactions.

Device training package

There were two further training requirements that were related specifically to the use of the device. All site staff who had a role in the application of the device were required to complete the following training before they undertook their role: (1) instructional $ECCO_2R$ videos and (2) onsite training sessions. Device training logs were only collected for staff recorded on the delegation log.

Instructional $ECCO_2R$ videos – sites were provided with a link to a webpage containing a set of online instructional $ECCO_2R$ videos. All delegated staff were required to complete and document this training on the study training log. A copy was then provided to the CTU for study records. There were seven videos in total (lasting approximately 5 minutes each), covering a range of device-specific areas:

- device setup and priming
- catheter insertion
- starting and managing therapy
- changing a cartridge
- ending therapy
- changing controller
- return of used components.

Onsite device training sessions – onsite device training sessions were provided to all sites initially, regardless of their experience with the $ECCO_2R$ device. The number of sessions requested was usually dependent on a site's experience or the size of the team involved in the study at that site. All staff at the site who were involved in the use of the device (e.g. doctors, nurses and ICU technicians) were required to attend sessions that were provided by the device manufacturer's support staff and REST trial research nurses.

Onsite sessions lasted approximately 3 hours and consisted of practical device training followed by the opportunity to ask questions and discuss the practical use of the device, with the device manufacturer's support team and research nurses. Multiple sessions would be held over the day or over several days depending on the size of the team in order to capture all staff. This was to facilitate staff shift changes and other factors, such as staff capacity and workload in ICU. These sessions were also the perfect opportunity to identify staff who would be willing to become 'Super Users' at the site; these staff would be given extensive hands on training using the device to ensure a higher level of understanding, which could then be disseminated through the site team as required.

Due to the nature of the device and the differing level of experience in the use of the device at sites, additional support was offered to sites when they opened to recruitment. Device manufacturer's support staff and the research nurses would endeavour to attend in person for a site's first two intervention patients to assist with administering the intervention and to ensure there were no issues or concerns. The support staff co-ordinated after randomisation to ensure they were present at the site within a short time frame to give hands on support with device insertion and $ECCO_2R$ application.

Lessons learnt from device training

The device training was a positive exercise and gave site staff a practical understanding of the device. Sites indicated that the format and flexibility of the sessions in conjunction with the ongoing follow-up support from the trainers was helpful in preparing them to undertake the study. Trainers noted that the question and answer sessions were positive and focused mainly around the logistics of what was needed to successfully run the trial at site, randomisation timings and what team resources would be needed. Sessions were well attended with site staff extremely engaged. In regards to the $ECCO_2R$ videos, feedback from sites was positive on the content of the videos and its relevance to the practical use of the device. Some sites reported an additional benefit, whereby clinicians would access the videos while completing the catheter insertion at the bedside, offering them additional confidence completing the process. The videos could be accessed through the study smart phone application for convenience.

At the start of the study, it was felt that the trial team resource required to undertake the onsite device training package was manageable, which in part was due to the staggered fashion in which sites were progressed onto the study. However, as the number of sites with varying experience in device use increased, there was a limitation in the availability of the external device manufacturers' support team and research nurses to facilitate new site training sessions and to provide additional support for first two intervention patients. There was also the additional pressure of continuing to provide support for inexperienced sites who, after undertaking the initial training, still required ongoing training due to issues, for example, change in staff and length of time between randomisations. This limitation was mainly due to the large number of sites that required ongoing support or external support staff not being able to travel to the site within the randomisation window for device connection. This, paired with the limitation of not being able to control the external company's availability, meant that there were a number of occasions where support was not available and site did not feel comfortable connecting the intervention.

Unfortunately, this resulted in a small number of patients not being recruited or receiving the intervention.

Online training programme

An e-learning course was created for REST and hosted on LearnPro® (Edinburgh, UK), an e-learning management system used by the NHS. The course contained two modules; a module focusing on the clinical aspects of the trial aimed at all medical, nursing and additional staff; and a module focusing on research activities aimed at research staff but could be completed by any interested staff member. Once the modules and assessments were completed, the user was then able to print a certificate off for their Continuing Professional Development portfolios. There was also a smart phone application to accompany the online platform, which provided reference material for convenience for sites when conducting the trial. These were updated as the trial progressed, however, as some technological issues were noted as the study progressed. These were due to login issues where certain site IT departments blocked access to the platform or issues with updated content which were only resolved when the user signed out and logged back in. Due to the platform's ease of use, sites were provided with e-learning user guides and a support application user guide to help them navigate the system rather than being provided training by the trial team. Access to a test environment was also provided in order to get an overview of the system prior to using in the live environment.

Lessons learnt from e-learning course

Overall, external feedback indicated that sites felt that the e-learning course was a useful study tool to aid and refresh staff in the study processes throughout the life of the study. A large number of staff confirmed that they had accessed the platform and found it useful, but some noted ongoing technical difficulties in accessing the system due to their IT departments. User report data from the LearnPro company reported a lot of centre variability of downloads of both the application and the modules, but all recruiting sites took advantage of its availability.

Internally, the provision of this platform required a great deal of administrative resource from the clinical lead, research nurses and the trial team to set up and maintain the content of the system along with responding and resolving ongoing queries and questions sites may have. There was also a significant financial cost, but it was felt that this was acceptable in order to provide this beneficial service for the users.

Acceptability of the intervention

Due to the complexity of the device and the varying experience of sites in the use of $ECCO_2R$, the chief investigator felt it important that the study had the support of the wider ICU team given the complexity and the exploratory nature of the device. Therefore, as part of the site setup, PIs were asked to confirm by e-mail that a discussion had taken place within their wider ICU community regarding the study and its intervention, and there was agreement internally to run the study. A copy of this e-mail was then retained in the Investigator Site File and Trial Master File.

Recruitment challenges and strategies

The REST trial contained a pilot phase initially which led into the main study phase. One of the target milestones in the pilot phase was to recruit 42 patients, which was successfully achieved. However, recruitment to the main study was below expectations, and the study was closed early due to futility, following recruitment of 412 out of the 1120 target sample. The pilot study had asked for 6–10 volunteer sites to follow the same processes as the main trial and aimed to determine protocol compliance, recruitment rates and data collection. The sites were chosen to reflect those participating in the main trial, although they may have overestimated recruitment as they were early trial adopters and potentially the best recruiters. Throughout the study, screening logs were kept by all sites in order to monitor and facilitate a review of the reasons for the inclusion and exclusion of patients to REST. The screening logs also collected miscellaneous reasons for non-recruitment that were not protocol-specified exclusion criteria. These were collected under the heading 'other'. Screening and recruitment data were extracted from the clinical database by the data manager on a monthly basis and reported to the trial management group for review. As a result of this ongoing review, a number of barriers to recruitment were identified:

- specific protocol inclusion/exclusion criteria adversely affecting recruitment due to clarity and poor understanding by site staff
- device/consumable issues affecting confidence
- lack of available device support for inexperienced sites
- connection issues/AEs in intervention patients affecting confidence
- available staff/resources at site
- lack of suitable patients.

A number of initiatives were implemented to try to address the challenges:

Inclusion/exclusion criteria issues

Several amendments to the protocol inclusion/exclusion criteria were made during the study to facilitate recruitment. These were:

- 'Patients not expected to survive 6 months on basis of premorbid health status' amended to 'Patients not expected to survive 90 days on basis of premorbid health status'.
- Clarification wording added to platelet exclusion – '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'.
- Clarification wording added to the Do Not Attempt Resuscitation exclusion – 'excluding advance directives'.

Device/consumable issues

As the study progressed and sites gained experience in the use of the device, a number of technical problems arose relating to device technical problems. Examples included: battery failure, CO_2 alarm warnings, cannula or guidewire suitability, calibration errors and equipment failure. The impact of these occurrences meant some sites (both experienced and inexperienced) began to lose confidence in using the device and had concerns over the safety of treating patients. In order to address these challenges, the trial team introduced a number of measures to attempt to reintroduce confidence in the device and restore clinical equipoise at the affected sites. Where the issue was a lack of confidence in the technical capabilities of the device and its consumables, the sites were offered additional training and support from the device manufacturer's support team or trial research nurses when connecting a patient to the device. The trial team created a tracking sheet to log all device incidents and the actions taken to resolve the incidents, and these were discussed with the manufacturer.

There were a small number of recurring issues identified, which were easily resolved by troubleshooting or by providing general guidance to sites. Other issues were then raised with the device manufacturer to identify solutions or seek guidance on how to avoid these issues happening again. Where necessary and possible, the device manufacturer provided technical support engineers, who went out to site to repair or replace the device. There were, unfortunately, limitations to the availability of the technical support engineers, which were unavoidable as they were external vendors and had additional work commitments. At all times, the trial team endeavoured to resolve issues quickly and put steps in place to try to avoid the issue recurring in the future, as there was the possibility that this could bring about negative discussions regarding the device within the sites and wider ICU community.

An additional initiative that was felt to be beneficial in helping to troubleshoot technical issues was to identify a 'Super User' at each site who was an experienced nursing staff member with a role to provide support and troubleshoot issues for the bedside team caring for patients allocated the intervention. These 'Super Users' had more in-depth knowledge and hands-on experience in the use of the device.

Connection issues/adverse events

Where the challenges related to a lack of confidence both in experienced and inexperienced sites due to AEs, ongoing support was provided to sites in terms of training or on-site visits during connections. The trial team would then also communicate with the wider ICU teams where requested to provide advice on connections and reassurance on the acceptability of the intervention. It was felt that it was important to address sites' concerns regarding AEs as this could then also determine the support of the wider ICU community and their support of the study. AEs were discussed routinely at monthly meetings of the PIs, and sites were allowed the time to explain and ask questions if concerned. Issues such as how to reduce complications on cannula insertion were discussed, and suggestions on how to improve technique were shared.

Lack of available device support for inexperienced sites

Where sites were identified as low recruiters or needing additional training, the support team/research nurses visited sites on a number of occasions to support and train the teams. The research nurses then followed up these visits by staying in close contact by telephone or e-mail to offer further motivation. Where a site had little previous experience in using the intervention, recruitment initially relied on how the intervention went with the first or second patient allocated to the intervention. Therefore, in order to address this and to ensure that sites felt supported in using the device, arrangements were put in place to have a representative from the device manufacturer's support team or research nurse team in attendance to assist the site while they were putting the participant onto the device. Dependent on the length of time between randomisations, this training had the potential to be continuous as sites

progressed through the study action plan which was put in place to identify, monitor and support low recruiting sites. This close contact and ongoing visits usually translated into an improvement in recruitment in these types of sites.

One further initiative that was introduced to offer support to low recruiting sites and to promote successful recruitment was to have experienced PIs, who had been identified by the trial team as promoting best practice within their ICU, to speak at the site investigator meetings held during national ICU meetings. The aim of the presentation at the investigator meeting was to give other sites an insight into how their site disseminated training, which focused mainly on a multidisciplinary collaborative approach to the REST trial.

Coenrolment

The REST trial promoted coenrolment where appropriate in keeping with UK guidance on coenrolment in critical care trials. There was an agreement to coenrol with over 50 studies where ethical approval was in place, and there was no biological interaction. Sites were encouraged to inform the trial team of studies in their unit who they wanted to coenrol. This was very successful with 76 patients recruited who were coenrolled with other studies. The trial management group oversaw the study coenrolment process and reviewed listings on a monthly basis to ensure that agreements were in place where required.

Motivational resources

- Communication – to promote study interest and recruitment at sites and to show sites' appreciation for their continued efforts, the trial team would send congratulatory e-mails to recruiting sites after each patient. Site PIs also received regular telephone calls from the clinical lead and chief investigator to thank for recruitment efforts and discuss ways in which the trial unit could assist if recruitment was poor.
- Prizes – the trial team awarded prizes quarterly to the best recruiting and screening sites, with additional prizes awarded to sites who recruited special target patients, such as the 100th patient. In order to include smaller sites, the trial team would award ad hoc prizes for the site staff member that went above and beyond in their study role.
- Promotional material – a range of promotional materials, for example, pens, highlighters, sticky notes and key rings, were provided to sites to raise the profile of the study and as a thank-you to the research teams at site.

Monthly site teleconferences

The trial team held monthly investigator meetings to help support sites and provide clarification on study matters where required. This meeting was also used to promote discussion within the sites so that sites who were recruiting well would pass on tips and aids that they have found successful.

The main objective of the monthly investigator meetings was that we could offer support and clarification to existing and new sites around study areas, for example, 'Eligibility Criteria' and 'AE/SAE Reporting'.

Investigator meetings at the national ICU conferences

The trial team would hold investigator meetings to coincide with national ICU meetings to encourage attendance and promote the study. These meetings were well attended and gave sites a chance to discuss the study and any positive or negative experiences they had had while running the study. The trial study felt that these meetings were beneficial in getting to meet site staff in person and promote a good working relationship between the trial team and site staff.

X/Twitter

A REST trial X [(formerly Twitter) X Corp., San Francisco, CA, USA] account was created to keep sites up to date on study progress and recruitment. The trial team would announce recruitment figures on the account to promote study awareness and to keep the sites up to date on recruitment at other sites. The main aim of this initiative was to promote healthy competition between study sites.

Open calls for new sites

Due to the ongoing action plan and the closure of poor recruiting sites, the trial team contacted the UK Clinical Research Network, in order to identify new sites to replace sites closed due to poor recruitment. This call was successful with a number of new sites identified. An advertisement was also placed in the Journal of the Intensive Care Society to see if any additional sites would be interested in joining the REST trial.

Newsletter

A newsletter was circulated to sites on a quarterly basis. The main objective of the newsletter was to update sites on study updates, new sites, FAQs, helpful pointers and target recruitment versus actual. The newsletter was also used to document prizes that were awarded to sites for recruitment and screening. Sites indicated that they found the newsletters helpful and informative.

Action plan for low recruiting sites

In order to promote recruitment, low recruiting sites were identified and progressed through an action plan, which aimed to provide sites with practical solutions and support to facilitate further recruitment. Where the implemented measures were successful and future device connections went well, sites usually went on to recruit well in the future. Where sites did not regain confidence, recruitment levels usually did not improve and sites were then progressed through the study action plan to closure. The action plan was formulated to help provide practical solutions to resolve issues that were identified at sites and improve their recruitment rate. The action place was divided into stages, and sites would progress through each stage depending on the time from the site opening or the time from when they last recruited a patient.

Stage 1: initial screening log assessment (+ 4 weeks open/recruited a patient)

The trial team would contact sites to discuss:

- screening activities
- issues identified
- formulate a plan with agreed timelines.

Stage 2: screening log and recruitment assessment (+ 8–12 weeks open)

The trial team would again contact sites to discuss:

- screening logs
- queries regarding eligible patients
- concerns regarding low recruitment
- teleconference with PI and research staff
- update plan with any new agreed timelines.

Stage 3: screening and recruitment assessment (+ 12 weeks)

Discussions between the trial team and the site involved an assessment of the quantity and characteristics of patients screened. An onsite visit from the research nurse was offered who would attend to discuss strategies, provide additional training or to assess sites interpretation of the inclusion/exclusion criteria.

Additional resources were also made available to sites going through the action plan, for example, PowerPoint® presentations to help train staff, shared experiences from other sites, feedback on communications and issues identified and notified to the trial team. In support of the plan, the chief investigator and clinical lead would also make monthly telephone calls to the PIs of the sites who have been identified as having continued low screening/recruitment data or any other additional concerns identified. These calls were also used to gauge site engagement and to discuss the identified issues in order to offer advice and promote plans of action.

It was hoped that the action plan and ongoing site communication would show an increase in recruitment over time; however, there were a number of sites that continued to under-recruit, therefore a discussion took place with the PI to discuss whether it was feasible to continue to run the study at their site. In total, there were 15 sites closed as a result of the action plan.

Lessons learnt from recruitment strategies

The recruitment strategies were implemented well by the trial team and were well received by sites. Unfortunately, the study did not reach its target recruitment, but we feel all resources were positive resources and would introduce these again in future studies.

Trial delivery conclusions

The REST was a large multicentre trial that inevitably had challenges and limitations both internally and externally in relation to several areas, for example, training, resources, costs, recruitment and collaboration with industrial partners. The trial team put in place robust processes and resources to deliver a training programme to over 51 UK sites using both online and onsite training in order to prepare sites to undertake the study successfully and confidently. Furthermore, as a trial team, we ensured that challenges with recruitment were quickly identified and addressed with processes put in place to promote recruitment. The remote aspect of the trial support provides a model for future studies and will help to potentially limit costs of trial delivery.

Patient and public involvement

Aim

The aim of including a patient and public involvement (PPI) person in all aspects of the study was to advise on the use of patient-centred outcomes that may have an impact on patients, from the design of the research application through to the dissemination of the study results.

Methods used

The study team worked with the PPI representative from the development of the research project right through to the dissemination of study results. The PPI representative was involved in several different

areas, including protocol, patient information sheet and consent form development along with advising on recruitment strategies and study progress as a member of the Trial Steering Committee.

Outcome of patient and public involvement

Patient and public involvement helped shape the overall design of the study, ensuring that the patient's perspective was at the forefront of all study considerations. PPI helped improve the overall quality and relevance of the research that was being undertaken, focusing on respect and any potential future patient benefits for the patients involved. PPI involvement ensured that the research participant information was provided in such a manner that was understandable to patients.

Equality, diversity and inclusion

The study enrolled 412 patients in the REST study from 51 ICUs in the UK NHS. Sixty-five per cent of recruited patients were males, and 35% were females. The study did not collect data on ethnicity groupings in order to ascertain whether the study participants were representative of the wider acute respiratory distress syndrome (ARDS) population. However, given the UK-wide (Northern Ireland, England, Scotland and Wales) geographical diversity of the ICUs involved in the study would indicate a diverse group of patients, ensuring that the study results were relatable.

Implication for decision-makers

The study adds to the evidence base about how we should aim to mechanically ventilate adult patients with hypoxaemic respiratory failure. The results show that there are no short- or long-term benefits with the addition of $ECCO_2R$ to facilitate lower tidal volume ventilation in moderately severe respiratory failure, and it should not be used outside the setting of clinical trials. Consideration should be given to discontinuing its use for this indication as it is not clinical or cost-effective, and its use can be associated with significant complications. This trial informed the European Society of Intensive Care Medicine guidelines for the management of ARDS.[17]

Research recommendations

The following research recommendations were generated across the threaded publications:

- It remains unknown whether a different population might benefit from $ECCO_2R$. Enrichment strategies to identify a population that may be more likely to benefit are needed for future trials of $ECCO_2R$.
- The core outcome set for studies evaluating survivors of acute respiratory failure was published after the REST trial had commenced.[18] Future studies should consider the adoption of this core outcome set.
- Future ICU trials should collect more multidimensional long-term outcomes, for example, patient's capacity to return to work.
- Measuring baseline HRQoL in critical care studies is difficult; future economic evaluations in this setting should consider measuring HRQoL as soon as possible after the patients regain capacity.
- Future studies should endeavour to record bleeding complications using common definitions, such as those proposed in the International Extracorporeal Membrane Oxygenation Network core outcomes set.[19]
- The effect of the intervention may vary with $PaO_2 : FiO_2$, although the evidence for this effect moderation was of low credibility. These variables could be used as physiological markers for predictive enrichment in future trials evaluating $ECCO_2R$.
- To account for heterogeneous effects, future clinical trials of $ECCO_2R$ could use predicted absolute risk reduction (computed from the model derived in Goligher *et al.*[20]) as a trial entry criterion or as a stratification variable in the analysis.

Overall conclusion

In conclusion, in a randomised clinical and cost-effectiveness trial, we were unable to find a benefit with the use of extracorporeal CO_2 to facilitate lower tidal volume ventilation in adult patients with AHRF. As there were no short- or long-term benefits found and the device is associated with cost and potentially significant complications, we would advise against using this device for this indication in addition to routine care of these patients.

Additional information

Contributions of authors

James J McNamee (http://orcid.org/0000-0002-2564-8511) (Clinical lead of the REST study): Conceptualisation (equal), Data curation, Formal analysis, Funding acquisation, Investigation, Methodology, Project administration, Visualisation. Writing - Original draft, Writing - Reviewing and editing.

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Andrew J Boyle (http://orcid.org/0000-0002-6201-805X) (Coinvestigator): Data curation, Formal analysis, Investigation, Methodology, Visulualisation, Writing - Original draft.

Colette Jackson (http://orcid.org/0000-0001-7814-0749) (Trial manager): Investigation, Project administration, Resources. Visualisation, Writing - Original draft.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives. You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data or trial materials may be granted following review.

Ethics statement

South Berkshire REC 16/SC/0089 (England, Wales and Northern Ireland); Scotland A REC 16/SS/0048 (Scotland) (14th March 2016).

Information governance statement

Belfast Health and Social Care Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, BHSCT is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (https://belfasttrust.hscni.net/about/access-to-information/data-protection/).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJDM0320

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Publications

McNamee JJ, Gillies MA, Barrett NA, Agus AM, Beale R, Bentley A. *et al.* pRotective vEntilation with veno-venouS lung assisT in respiratory failure: a protocol for a multicentre randomised controlled trial of extracorporeal carbon dioxide removal in patients with acute hypoxaemic respiratory failure. *J Intensive Care Soc* 2017;**18**:159–69. https://doi.org/10.1177/1751143716681035

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List of abbreviations

AE	adverse event
AHRF	acute hypoxaemic respiratory failure
ARDS	acute respiratory distress syndrome
$ECCO_2R$	extracorporeal carbon dioxide removal
HRQoL	health-related quality of life
ICU	intensive care unit
ISRCTN	International Standard Randomised Controlled Trial Number
IT	information technology
PI	principal investigator
REST	pRotective vEntilation with veno-venouS lung assisT in respiratory failure
SAE	serious adverse event

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Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial

McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, *et al*. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial. *JAMA* 2021;**326**(11):1013–23. https://doi.org/10.1001/jama.2021.13374

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Extracorporeal carbon dioxide removal in acute hypoxaemic respiratory failure: a systematic review, Bayesian meta-analysis and trial sequential analysis

Millar JE, Boyle AJ, Drake TM, Adams CE, Glass AW, Blackwood B, *et al*. Extracorporeal carbon dioxide removal in acute hypoxaemic respiratory failure: a systematic review, Bayesian meta-analysis and trial sequential analysis. *Eur Respir Rev* 2022;**31**:220030. https://doi.org/10.1183/16000617.0030-2022

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Acute hypoxaemic respiratory failure after treatment with lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal: long-term outcomes from the REST randomised trial

Boyle AJ, McDowell C, Agus A, Logan D, Stewart JD, Jackson C, *et al*. Acute hypoxaemic respiratory failure after treatment with lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal: long-term outcomes from the REST randomised trial. *Thorax* 2023;**78**:767–74. https://doi.org/10.1136/thorax-2022-218874

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Extracorporeal carbon dioxide removal compared to ventilation alone in patients with acute hypoxaemic respiratory failure: cost-utility analysis of the REST RCT

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Abstract

Extracorporeal carbon dioxide removal compared to ventilation alone in patients with acute hypoxaemic respiratory failure: cost-utility analysis of the REST RCT

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Background: Acute hypoxaemic respiratory failure requiring mechanical ventilation is a major cause of morbidity and mortality and has significant resource implications in terms of intensive care unit and hospital stay.

Objective: To assess the cost-effectiveness of extracorporeal carbon dioxide removal compared to ventilation alone in patients with acute hypoxaemic respiratory failure.

Design: A cost-utility analysis embedded within a pragmatic, multicentre, allocation-concealed, open-label, randomised controlled trial.

Participants: Four hundred and twelve (of a planned sample size of 1120) adult patients receiving mechanical ventilation for acute hypoxaemic respiratory failure, were recruited between May 2016 and December 2019 from 51 intensive care units in the UK.

Interventions: Participants were randomised (1 : 1) to receive extracorporeal carbon dioxide removal for at least 48 hours (n = 202) or standard care with ventilation alone (n = 210).

Outcomes: Health-related quality of life via the EuroQol-5 Dimensions, five-level version, health resource use and associated costs were measured over the study period. The cost per quality-adjusted life-year was estimated at 12 months post randomisation.

Results: Mean EuroQol-5 Dimensions, five-level version utility scores were low and similar for each group. Quality-adjusted life-years were calculated for those patients with complete EuroQol-5 Dimensions, five-level version data (extracorporeal carbon dioxide removal n = 140, ventilation alone n = 143) and there was no discernible difference in quality-adjusted life-years at 12 months (mean difference −0.01; 95% confidence interval −0.06 to 0.05; 140). Total 12-month health resource use cost (including intervention costs) was calculated for those patients with complete cost data (extracorporeal carbon dioxide removal n = 125, ventilation alone n = 126) and costs were statistically significantly higher in the extracorporeal carbon dioxide removal group (mean difference £7668.76, 95% confidence interval 159.75, 15,177.77). Multiple imputation was used for missing total cost and quality-adjusted life-year data in the cost-utility analysis. Ventilation alone dominated extracorporeal carbon dioxide removal and there was 0% probability of extracorporeal carbon dioxide removal being cost-effective compared to ventilation alone for all willingness to pay thresholds per quality-adjusted life-year considered (£0–50,000).

Conclusions: Extracorporeal carbon dioxide removal was associated with significantly higher costs, but no benefit in health-related quality of life. Given the data, extracorporeal carbon dioxide removal is not considered to be a cost-effective approach to treating patients with acute hypoxaemic respiratory failure.

Limitations: These included the absence of a baseline healthy utility score, minor data loss related to not obtaining complete intensive care unit readmission data for Scottish participants, and not estimating long-term cost-effectiveness due to the study closing early.

Future work: Measuring baseline health-related quality of life in critical care studies is difficult; future economic evaluations in this setting should consider measuring health-related quality of life as soon as possible after the patients regain capacity.

Trial registration: This trial is registered as NCT02654327 and ISRCTN 31262122.

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List of abbreviations

AHRF	acute hypoxaemic respiratory failure
APACHE II	acute physiology and chronic health evaluation II
CEAC	cost-effectiveness acceptability curve
CMP	case mix programme
eDRIS	electronic Data Research and Innovation Service
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
$ECCO_2R$	extracorporeal carbon dioxide removal
GP	general practitioner
HRQoL	health-related quality of life
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
ICNARC	Intensive Care National Audit and Research Centre
ICU	intensive care unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PSS	personal social services
QALY	quality-adjusted life-year
REST	pRotective vEntilation with veno-venouS lung assisT in respiratory failure
SICSAG	Scottish Intensive Care Society Audit Group
WTP	willingness to pay

Introduction

Acute hypoxaemic respiratory failure (AHRF) requiring mechanical ventilation is a major cause of morbidity and mortality and has significant resource implications in terms of intensive care unit (ICU) and hospital stay.[1–3] The average cost per ICU bed-day exceeds £1800[4] and delivery of critical care to patients with AHRF accounts for a significant proportion of ICU capacity with an average length of stay of approximately 15 days.[5] In addition, survivors often have long-term physical and cognitive impairment requiring support in the community after hospital discharge. The high incidence, mortality, long-term consequences and high economic costs mean that AHRF is an extremely important problem.[1–3]

The clinical findings from the pRotective vEntilation with veno-venouS lung assisT in respiratory failure (REST) trial[6] reported that extracorporeal carbon dioxide removal ($ECCO_2R$) did not significantly reduce 90-day mortality or ventilator-free days compared to ventilation alone (standard care) and more serious adverse events occurred in the intervention group. However, the National Institute for Health and Care Excellence (NICE) recommends that the effects of an intervention on health-related quality of life (HRQoL) should also be quantified to allow the calculation of quality-adjusted life-years (QALYs) and the evaluation of cost-effectiveness.[7] Evidence on the cost-effectiveness of $ECCO_2R$ is lacking.[8] A recent preliminary model-based analysis[9] reported $ECCO_2R$ may be cost-effective in the treatment of acute respiratory distress syndrome, but further data from clinical trials and observational studies are required to support this finding. The aim of this paper is to report on the findings of a cost-utility analysis to assess the cost-effectiveness of $ECCO_2R$ compared to ventilation alone in patients with AHRF.

Methods

A within-trial cost-utility analysis was embedded within the REST trial[6] to determine whether $ECCO_2R$ and lower tidal volume mechanical ventilation are cost-effective at 12 months post randomisation compared to standard care with conventional lung protective mechanical ventilation alone in patients with acute hypoxaemic respiratory failure in the critical care setting. The incremental cost-effectiveness ratio (ICER) was the cost per QALY. Initially, the aim of the REST economic analysis was to assess cost-effectiveness at both 12 months and over the lifetime of the patients using a de novo decision model. However, owing to the limitations of available data resulting from the trial being stopped early, the economic analysis was changed from those described in the original protocol and a decision model was not undertaken. Current guidelines for conducting[7,10,11] and reporting[12] economic evaluations were followed. The analysis was performed from the perspective of the National Health Service (NHS) and personal social services (PSS).[7] Discounting was not required for the analysis as the time horizon for analysis did not exceed one year.

Measurement of health resource use and costs

Hospital resource use data were collected prospectively using the case report form during the participants' primary admission. Length of stay for the primary critical care admission was calculated from the date of randomisation to the date of critical care discharge or date of death if this occurred within critical care. General hospital ward length of stay was calculated from the date of critical care discharge to the date of hospital discharge or date of death if this occurred on the ward. For ICUs that participate in the case mix programme (CMP), additional information was obtained from the Intensive Care National Audit and Research Centre (ICNARC) on any readmissions to critical care. For the four Scottish, non-CMP ICUs the intention had been to obtain this data from the Scottish Intensive Care Society Audit Group (SICSAG) via the electronic Data Research and Innovation Service (eDRIS) but unfortunately the application to obtain this data was delayed and data linkage could not be obtained prior to the early closure of the study. This meant data on readmission to critical care was unavailable for some participants.

To facilitate the costing of the critical care admissions the Healthcare Resource Group (HRG) codes corresponding to each critical care admission and any readmission during the primary hospital admission were provided by ICNARC for the CMP sites. The HRG codes represented the highest level of complexity, based on the total number of organs supported during the admission. Scotland has not fully adopted the HRG methodology, so for a consistent costing approach we applied the modal HRG code observed for the critical care admissions of participants at the CMP sites to the critical care admissions for the Scottish participants. Critical care costs were calculated by multiplying the unit cost associated with the HRG by the length of stay for that admission. The unit costs associated with the HRGs were obtained from the National Schedule of NHS Costs 2018/19[4] (see *Appendix 1*, *Table 5*). Ward stay costs were calculated by multiplying the number of ward days during the primary hospital admission by the unit cost associated with rehabilitation for respiratory disorders.

Participants' use of health and social care services from hospital discharge to 12 months was captured via a postal questionnaire completed at 6 and 12 months post randomisation. Telephone completion was also used for non-responders. Participants were provided with a health service log booklet at hospital discharge and again at 6 months to encourage them to keep track of their health resource use and facilitate questionnaire completion. Mortality status was confirmed prior to participant contact by contacting general practitioners (GPs).

Individual-level resource use was combined with unit costs to estimate costs for each participant. Unit costs were obtained from publicly available sources; National Schedule of NHS Costs[4] and Unit Cost of Health and Social Care from PSS Research Unit.[13] The cost of supplying oxygen at home was provided by the Northern Ireland Health and Social Care Board and costs for intervention consumables were obtained directly from Alung, the device provider. The last follow-up data was collected in 2019 and the price year was set at 2018/2019 (see *Appendix 1*, *Table 5*).

Measurement of health outcomes

The outcome of interest in the cost-effectiveness analysis was the QALY, a generic HRQoL measure. Utilities for the calculation of the QALYs were obtained using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L)[14] administered at 6 and 12 months post randomisation via a postal questionnaire. Telephone completion was also used for non-responders. The EQ-5D-5L is a generic preference-based measure of HRQoL, which provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with five levels of severity. Responses were converted into utility scores using the Crosswalk Value Set[15] for the UK population. This tariff maps the EQ-5D-5L responses on to the EuroQol-5 Dimensions, three-level version (EQ-5D-3L) and is currently the approach recommended by NICE.[16] QALYs were calculated using the area under the curve method. As patients were critically ill at baseline, an EQ-5D-5L utility score of zero was assumed, in keeping with other studies in the critical care setting.[5,17,18]

Analysis of health resource use, costs and outcomes

The descriptive statistics were used to summarise (by treatment arm) the resource use (during primary hospital admission and after discharge until 12 months), the associated costs, EQ-5D-5L scores and QALYs. Death was not treated as a censoring event and periods after death were counted as observations with known outcome[19] an approach used previously in similar patient populations[5,18] This meant that for participants who had died in hospital, resource use and EQ-5D-5L scores after hospital discharge until 12-month follow-up were considered to be zero. For patients who died between hospital discharge and 6 months resource use and EQ-5D-5L scores from 6 to 12 months were considered to be zero. Total costs and QALYs were analysed using linear regression. Significance ($p < 0.05$) was judged where the confidence intervals (CIs) excluded zero. Analyses were undertaken using Stata 15/IC for Windows® (StataCorp LP, College Station, TX, USA).

Cost-effectiveness analysis

Trial-based economic evaluations tend to measure participants' health resource use and health outcomes at multiple time over the duration of the study using self-complete questionnaires. As a result, missing data is a common problem due to reasons such as non-returns or loss to follow up. This has the potential to introduce bias into the results as participants with incomplete health economic data may be systematically different from those with complete data.[20] Therefore for the cost-effectiveness analysis we imputed missing total cost and QALY data using multiple imputation with chained equations and predictive mean matching using the 'mi impute chained command' in Stata. This assumes that data are missing at random (MAR). This involved a regression model being specified to predict the missing total cost and QALY data: treatment group, baseline acute physiology and chronic health evaluation II (APACHE II) score, age, mortality at 28 days and primary hospital admission costs were entered into the model as predictors. Forty imputed data sets were generated, which was similar to the maximum percentage of incomplete cases observed (40%) in the data as recommended by White *et al.*[21] The 'mi estimate' Stata command was used to facilitate the analysis of each of the imputed data sets and then combine the results. Linear regression was used to estimate the incremental (differential) mean costs and QALYs. The ICER was calculated by dividing the incremental mean costs by the incremental mean QALYs to estimate the cost per QALY. As negative ICERs are not meaningful, if this occurred we stated whether the intervention was dominant (i.e. more effective and less costly than standard care) or was dominated (less effective and more costly than standard care).

Uncertainty in the cost and QALY data was explored by the non-parametric bootstrapping of the linear regression cost and QALY models simultaneously, drawing 1000 samples of the same size as the original sample with replacement.[22] The resulting 1000 ICER replicates were plotted on the cost-effectiveness plane,[23] and used to construct a cost-effectiveness acceptability curve (CEAC).[24] This showed the probability of ECCO$_2$R being cost-effective compared to ventilation alone at various willingness to pay (WTP) per QALY thresholds. In general NICE considers interventions with an ICER of <£20,000 to be cost-effective.[7]

The incremental net monetary benefit (INMB) was also used to aid interpretation. The INMB is a summary statistic representing the value of an intervention in monetary terms when a WTP threshold for a unit of benefit is known. This was calculated by multiplying the incremental mean QALY by NICE's threshold of £20,000 and then subtracting the incremental mean costs. A positive INMB indicates the intervention is cost-effective.[10]

Sensitivity analysis for the cost-effectiveness analysis

The robustness of the results from the cost-effectiveness analysis was explored via the following sensitivity analyses: adjusting for baseline age and APACHE II score via multiple regression; reducing the time horizon of the cost-effectiveness analysis to 6 months, and scenarios of plausible departures from the MAR assumption. The latter was done via pattern-mixture models implemented using multiple imputation.[25] The impact of the following scenarios was explored: participants with missing QALY data were assumed to have worse HRQoL (10%) than those with observed QALY data; participants with missing cost data were assumed to have higher costs (10%) than those with complete cost data; and those with missing QALY and cost data were assumed to have both lower QALYs and higher costs.

Results

In total 412 participants were randomised; 202 to receive ECCO$_2$R and 210 to receive ventilation alone. Levels of missing health economic data by type and treatment group are in *Table 1*. These were similar between groups for all data types.

TABLE 1 Number (%) of participants with complete health economic data by type and treatment group[a]

Data type	$ECCO_2R$ (*n* = 202)		Ventilation alone (*n* = 210)	
	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)
Health resource				
Primary hospital admission (randomisation to hospital discharge)	193 (95.5)	9 (4.5)	202 (96.2)	8 (3.8)
Discharge to 6 months	149 (73.8)	53 (26.2)	150 (71.4))	60 (28.6)
6–12 months	154 (76.2)	48 (23.8)	154 (73.3)	56 (26.7)
Randomisation to 12 months	125 (61.9)	77 (38.1)	126 (60.0)	84 (40.0)
EQ-5D-5L				
6 months	162 (80.2)	40 (19.8)	161 (76.7)	49 (23.3)
12 months	150 (74.3)	52 (25.7)	155 (73.8)	55 (26.2)
QALYs at 12 months	140 (69.3)	62 (30.7)	143 (68.1)	67 (30.9)

a Death was not treated as a censoring event so zero service use and zero EQ-5D-5L scores were assigned where appropriate and the data was considered complete in these cases.

Health resource use and costs

Resource use during the primary admission is presented in *Appendix 1*, *Table 6* and self-reported health service use from hospital discharge to 12 months is presented in *Appendix 1*, *Tables 7* and *8*. Data is presented for all patients with available data without imputation of missing cases, by treatment arm. The costs (Great British pounds) associated with resource use are presented in *Table 2*. There was a trend for patients receiving $ECCO_2R$ to require marginally longer primary ICU stay, more ICU readmission days and more ward days than those receiving ventilation alone; however, none of these differences were statistically significantly different and the overall difference in primary admission costs (excluding intervention costs) was also not significantly different (mean difference £2666.97; 95% CI −2886.42 to 8220.35). The cost difference for the period from discharge to 6 months was relatively small (mean difference £172.70; 95% CI −871.81 to 1217.21), but a larger and statistically significant difference for the 6- to 12-month period (mean difference £858.52; 95% CI 125.83 to 1591.22) was observed. The resource use and costs associated with $ECCO_2R$ were also considered. These consisted of a cartridge for the Alung device (£3000 per patient) and a catheter (£650 per patient) and this total cost of £3650 was added to the total for each patient in the $ECCO_2R$ arm. Total health service use costs (including intervention costs) over the full 12 months were calculated for those patients with complete cost data (125 $ECCO_2R$ patients and 126 ventilation alone patients). The difference was large and statistically significantly different (£7668.76, 95% CI 159.75 to 15,177.77).

Health utility scores and QALYs

Mean EQ-5D-5L utilities and QALYs over the study period are presented in *Table 3* for patients with available data. Overall mean utility scores were low and similar for each group at both 6 and 12 months with no discernible difference in QALYs (mean difference −0.01; 95% CI −0.06 to 0.05).

Cost-effectiveness analysis

The results of the cost-effectiveness analysis for the base-case analysis and the sensitivity analyses are presented in *Table 4*. For all scenarios $ECCO_2R$ was associated with lower QALYs compared to ventilation alone, but the differences were small and not statistically significant indicating broad equivalence in terms of HRQoL impact. However, statistically significantly higher health-care costs were observed with $ECCO_2R$ compared to ventilation alone and so $ECCO_2R$ can be described as being dominated by ventilation alone and not cost-effective given the data. Uncertainty in the cost and QALYs estimates was

TABLE 2 Total costs (UK £) by type and treatment group over 12 months (observed cases, without imputation of missing data)

Health resource costs	$ECCO_2R$ (*n* = 202)		Ventilation alone (*n* = 210)		Mean difference (95% CI) $ECCO_2R$ – ventilation alone
	Obs	Mean (95% CI)	Obs	Mean (95% CI)	
Primary ICU stay	202	30,846.73 (26,200.92 to 354,92.55)	210	28,404.31 (25,354.45 to 31,454.17)	2442.42 (−3057.37 to 7942.21)
Other ICU readmission days	202	2584.77 (1073.83 to 4095.71)	210	822.21 (184.03 to 1460.40)	1762.56 (149.09 to 3376.03)
Wards days	193	4310.21 (3049.48 to 5570.94)	202	3843.62 (2841.85 to 4845.40)	466.58 (−1131.20 to 2064.37)
Total primary admission costs	193	35,242.26 (30,989.03 to 39,495.50)	202	32,575.30 (28,950.86 to 36,199.73)	2666.97 (−2886.42 to 8220.35)
Intervention	**202**	**3650 (0)**	**210**	**0 (0)**	3650 (0)
Health service use discharge to 6 months	149	2070.65 (1376.05 to 2765.25)	150	1897.95 (1112.72 to 2683.18)	172.70 (−871.81 to 1217.21)
Health service use 6–12 months	154	1531.92 (850.77 to 2213.07)	154	673.40 (395.60 to 951.20)	858.52 (125.83 to 1591.22)
Total health-care costs over 12 months	125	40,292.58 (34,390.4 to 46,194.70)	126	32,623.82 (27,911.58 to 37,336.06)	7668.76 (159.75 to 15,177.77)

CI, confidence interval; *N* (%), number of participants using the service; *n*, number randomised; Obs, observed number of cases.

TABLE 3 Mean (95% CI) EQ-5D-5L utilities and QALYs, by treatment group (observed cases, without imputation of missing data)

Time point	$ECCO_2R$ (*n* = 202)		Ventilation alone (*n* = 210)		Difference (95% CI) $ECCO_2R$ – ventilation alone
	Obs	Mean (95% CI)	Obs	Mean (95% CI)	
6-month utility	162	0.23 (0.18 to 0.28)	161	0.23 (0.18 to 0.29)	−0.00 (−0.08 to 0.07)
12-month utility	150	0.24 (0.18 to 0.29)	155	0.24 (0.19 to 0.30)	−0.01 (−0.09 to 0.08)
QALYs at 12 months[a]	140	0.15 (0.11 to 0.19)	143	0.16 (0.12 to 0.20)	−0.01 (−0.06 to 0.05)

Obs, observed number of cases.
a A utility of zero was assigned to all patients at baseline for the calculation of QALYs.

TABLE 4 Results of the cost-utility analyses (including all participants with missing data imputed)

Analyses	Total costs (£) (mean, 95% CI)		QALY (mean, 95% CI)		Mean incremental costs (95% CI)	Mean incremental QALYs (95% CI)	ICER[a]	INMB[b] (£) (mean, 95% CI)
	$ECCO_2R$ (n = 202)	Ventilation alone (n = 210)	$ECCO_2R$ (n = 202)	Ventilation alone (n = 210)				
Base-case analysis	42,755.11 (38,541.62 to 46,968.59)	34,855.02 (30,751.14 to 38,958.91)	0.211 (0.169 to 0.253)	0.220 (0.174 to 0.265)	7900.08 (2008.48 to 13,791.68)	−0.008 (−0.052 to 0.035)	Dominated	−8069.25 (−13,741 to −2396.73)
Sensitivity analyses								
Adjusting for baseline age and APACHE II score	42,579.54 (38,352.34 to 46,806.73)	35,022.77 (30,905.08 to 39,140.46)	0.210 (0.168 to 0.252)	0.221 (0.176 to 0.266)	7556.77 (1695.29 to 13,418.25)	−0.011 (−0.053 to 0.032)	Dominated	−7770.74 (−13,418.74 to −2122.73)
6 months time horizon	40,972.04 (36,846.58 to 45,097.51)	34,585.23 (30,543.72 to 38,626.74)	0.069 (0.056 to 0.082)	0.072 (0.058 to 0.086)	6386.81 (538.76 to 12,234.87)	−0.003 (−0.018 to 0.012)	Dominated	−6445.44 (−12,229.49 to −661.40)
Missing not at random (MNAR), −10% QALYs	42755.11 (38,541.62, 46968.59)	34,855.02 (30,751.14 to 38,958.91)	0.201 (0.161 to 0.241)	0.209 (0.166 to 0.251)	7900.08 (2008.48 to 13,791.68)	−0.008 (−0.050 to 0.035)	Dominated	−8054.00 (−13,731.66 to −2376.35)
+10% Costs	44,420.99 (40,021.53 to 48,820.46)	36,305.57 (32,022.24 to 40,588.91)	0.211 (0.169 to 0.253)	0.220 (0.174 to 0.265)	8115.42 (1980.32 to 14,250.52)	−0.008 (−0.052 to 0.035)	Dominated	−8284.59 (−14,199.13 to −2370.05)
−10% QALYs and +10% Costs	44,420.99 (40,021.53 to 48,820.46)	36,305.57 (32,022.24 to 40,588.91)	0.201 (0.161 to 0.241)	0.209 (0.166 to 0.251)	8115.42 (1980.32 to 14,250.52)	−0.008 (−0.050 to 0.035)	Dominated	−8269.34 (−14,192.10 to −2346.59)

a Negative ICERs do not convey any meaning and so values are not presented.
b INMB calculated at a ceiling ratio of £20,000 per QALY.

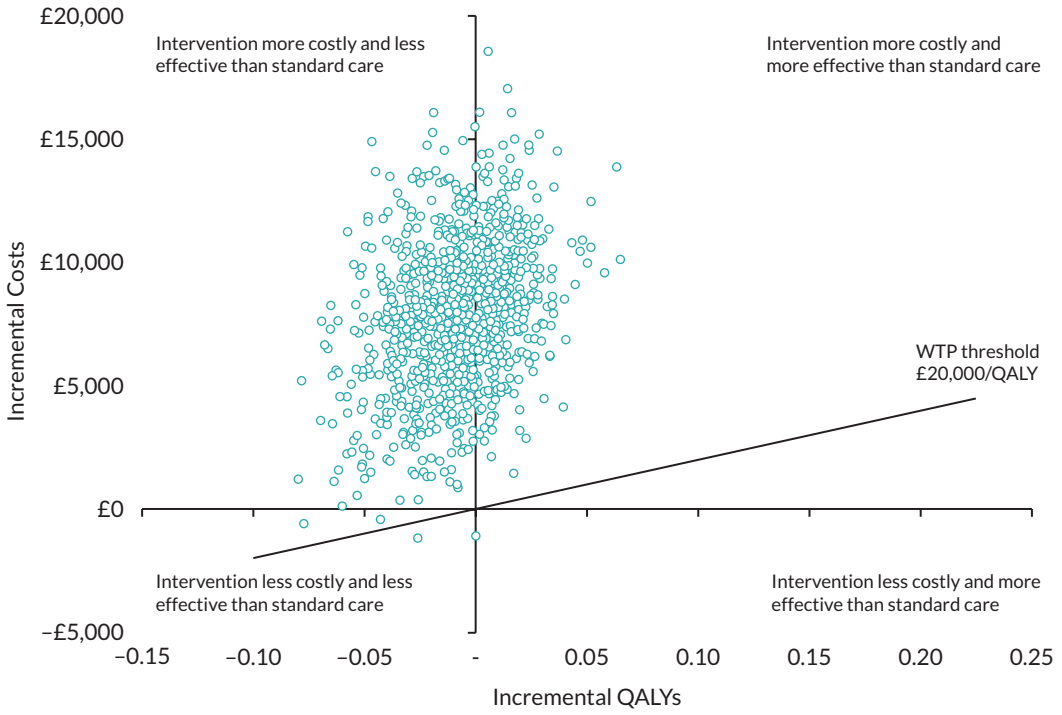

FIGURE 1 Cost-effectiveness plane for the base-case cost-utility analysis showing 1000 bootstrapped replications of incremental mean costs and QALYs and the WTP threshold of £20,000/QALY.

explored by displaying the results of the non-parametric bootstrapping on the cost-effectiveness plane for the base-case analysis (see *Figure 1*). It can be seen that ICER replicates straddle the north-west and north-east quadrants reflecting the consistently higher costs associated with $ECCO_2R$ in the data, and similarity in QALYs. The CEAC (see *Figure 2*) is in fact a line running along the *x*-axis indicating that there was 0% probability of $ECCO_2R$ being cost-effective compared to ventilation alone for any of the WTP threshold per QALY we considered (£0–50,000) in the analysis. The negative INMBs reflect that the intervention is not cost-effective compared to standard care at a WTP threshold of £20,000.

Discussion

The results showed that $ECCO_2R$ was associated with statistically significantly higher health-care costs compared to ventilation alone, with the intervention itself (£3650 per patient) contributing to approximately half of the incremental costs. The additional costs were not offset by any benefits since no difference in QALYs occurred between groups, indicating that the intervention had no impact on the HRQoL participants. The CEAC showed that there was 0% probability of $ECCO_2R$ being cost-effective compared to ventilation alone for any of the WTP thresholds per QALY considered (£0–50,000), given the data, and this finding was robust to sensitivity analyses.

Strengths of the analysis included the measures we took to handle missing data. As anticipated, there was varying degrees of missingness in the economic data collected from baseline to 12 months. We assigned zero utility scores and zero costs to participants who had died and employed multiple imputation for the cost-effectiveness analysis, therefore maximising the use of the available data. There was <5% missing data observed in the resource use collected during the participants' primary admission, thus our cost estimates are a meaningful addition to the cost of illness literature in the critical care population.

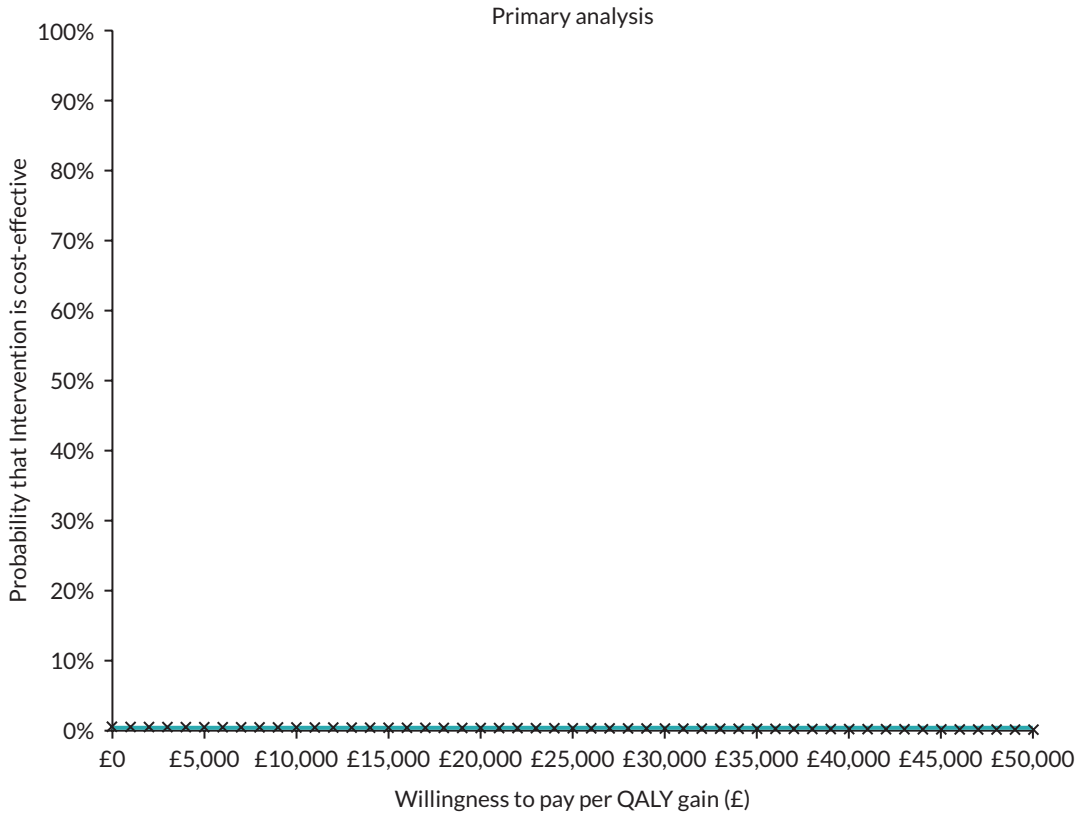

FIGURE 2 Cost-effectiveness acceptability curve showing the probability of intervention being cost-effective compared to standard care (base-case analysis).

There were a number of limitations to the analysis. Since participants were critically ill and ventilated at baseline we did not measure their HRQoL with the EQ-5D-5L. Instead we assigned all participants' baseline utility score zero in keeping with previous studies in the critical care setting. Since HRQoL was only measured at 6 and 12 months post randomisation, any short-term impact of the intervention on health participants' health may have gone undetected. Future studies should consider measuring HRQoL as soon as possible after the participants have regained capacity. We were unable to obtain data from SICSAG via eDRIS on Scottish participants. This meant we did not have information on any readmission to ICU they may have had during their primary admission. This would probably only have led to minor data loss since it only applied to 35 participants and only 17 participants from the remaining sample were readmitted to ICU. We did not include the additional staff time associated with the application of $ECCO_2R$, therefore the cost of $ECCO_2R$ is likely to be underestimated. Participants who did not return their follow-up questionnaires by post were given the opportunity to complete via telephone which may have introduced response bias. Finally, the economic evaluation had originally intended to estimate long-term cost-effectiveness of $ECCO_2R$ via a de novo decision model. Unfortunately the study closed early, limiting the data available to inform the model. Despite these limitations, the findings from this economic evaluation make an important contribution to the existing evidence base on $ECCO_2R$ therapy.

Conclusion

Extracorporeal carbon dioxide removal was associated with significantly higher costs, but no benefit in HRQoL. Given the data, $ECCO_2R$ is not considered to be a cost-effective approach to treating patients with acute hypoxaemic respiratory failure.

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Contributions of authors

Ashley Agus (https://orcid.org/0000-0001-9839-6282) (Senior Health Economist) designed and performed the economic evaluation, interpreted the analysis and drafted the manuscript.

James J. McNamee (https://orcid.org/0000-0002-2564-8511) (Consultant in Intensive Care Medicine) conceived the main study, interpreted the analysis and helped to revise the manuscript.

Colette Jackson (https://orcid.org/0000-0001-7814-0749) (Trial Manager) coordinated the acquisition of the data and helped to revise the manuscript.

Danny F. McAuley (https://orcid.org/0000-0002-3283-1947) (Professor and Consultant in Intensive Care Medicine) conceived the main study, interpreted the analysis and helped to revise the manuscript. All authors approved the final version of the manuscript. All authors vouch for the integrity, accuracy and completeness of the data.

Ethics statement

South Berkshire REC 16/SC/0089 (England, Wales and Northern Ireland); Scotland A REC 16/SS/0048 (Scotland).

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data or trial materials may be granted following review.

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Appendix 1

TABLE 5 Unit costs (£, UK) of critical care and health resource use

Resource item/HRG code	Unit cost (£)	Details	Source
XC01Z	2281	Adult Critical Care, 6 or more Organs Supported	National Schedule of NHS Costs 2018/19[4]
XC02Z	2097	Adult Critical Care, 5 Organs Supported	National Schedule of NHS Costs 2018/19[4]
XC03Z	1967	Adult Critical Care, 4 Organs Supported	National Schedule of NHS Costs 2018/19[4]
XC04Z	1764	Adult Critical Care, 3 Organs Supported	National Schedule of NHS Costs 2018/19[4]
XC05Z	1575	Adult Critical Care, 2 Organs Supported	National Schedule of NHS Costs 2018/19[4]
XC06Z	1152	Adult Critical Care, 1 Organ Supported	National Schedule of NHS Costs 2018/19[4]
XC07Z	933	Adult Critical Care, 0 Organs Supported	National Schedule of NHS Costs 2018/19[4]
Post-ICU ward day	351	VC40Z Rehabilitation for Respiratory Disorders	National Schedule of NHS Costs 2018/19[4]
GP surgery consultation	39	Based on 9.22 minute consultation	National Schedule of NHS Costs 2018/19[4]
GP phone consultation	15.52	Based on a 4 minute call	Unit Costs of Health and Social Care[7]
GP home consultation	99.45	11.4 minute consultation and 12 minutes travel time	Unit Costs of Health and Social Care[7]
GP out-of-hours consultation	99.45	Assumed the same cost as home consultation	Unit Costs of Health and Social Care[7]
GP nurse surgery consultation	10.85	Based on 15.5 minute appointment	Unit Costs of Health and Social Care[7]
GP nurse phone consultation	7.80	Based on 6.56 minute call	Unit Costs of Health and Social Care[7]
District nurse visit	46	Band 6	Unit Costs of Health and Social Care[7]
Specialist nurse visit	55	Band 7	Unit Costs of Health and Social Care[7]
Social worker visit	51		Unit Costs of Health and Social Care[7]
Physiotherapist visit	45	Band 6	Unit Costs of Health and Social Care[7]
Occupational therapist visit	48		Unit Costs of Health and Social Care[7]
Dietitian visit	46	Band 6	Unit Costs of Health and Social Care[7]
Counsellor visit	45	Band 6	Unit Costs of Health and Social Care[7]
Home help/carer visit	23		Unit Costs of Health and Social Care[7]
Emergency department attendance			
Attendance, not admitted	171	Weighted average non-admitted (excluding dead on arrival)	National Schedule of NHS Costs 2018/19[4]
Attendance, admitted	247	Weighted average admitted (excluding dead on arrival)	National Schedule of NHS Costs 2018/19[4]

continued

TABLE 5 Unit costs (£, UK) of critical care and health resource use (*continued*)

Resource item/HRG code	Unit cost (£)	Details	Source
Ambulance	257		National Schedule of NHS Costs 2018/19[4]
Outpatient visit	135	Weighted average of all outpatient attendances	National Schedule of NHS Costs 2018/19[4]
Hospital bed day	413	Weighed mean of non-elective admissions, divided by weighted average length of stay of non-elective admissions.	National Schedule of NHS Costs 2018/19[4] (Length of stay obtained through freedom of information request to NHS; FOI – 2104-1442254 NHSE:0426102)
Oxygen	1239	Per annum, includes installation, high flow concentrator, ambulatory cylinders and electricity.	Northern Ireland Health and Social Care Board personal communication.
$ECCO_2R$ intervention			
Cartridge	3000	Per patient	Alung communication
Catheter	650	Per patient	Alung communication

TABLE 6 Primary hospital admission resource use by treatment group (observed cases, without imputation of missing data)

	$ECCO_2R$ (*n* = 202)		Ventilation alone (*n* = 210)		
	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Mean difference (95% CI)
Primary ICU stay days	202	18.21 (15.72 to 20.69)	210	16.31 (14.64 to 17.97)	1.90 (−1.06 to 4.86)
Other ICU readmission days	202	0.35 (0.11 to 0.60)	210	0.16 (0.00 to 0.32)	0.19 (−0.10 to 0.48)
Ward days	193	12.28 (8.69 to 15.57)	202	10.95 (8.10 to 13.80)	1.33 (−3.22 to 5.88)
Hospital length of stay	193	29.59 (25.05 to 34.14)	202	27.16 (23.31 to 31.00)	2.43 (−3.48 to 8.35)

CI, confidence interval; *N* (%), number of participants using the service; *n*, number randomised; Obs, observed number of cases.

TABLE 7 Health resource use from hospital discharge to 6 months by treatment group (observed cases, without imputation of missing data)

	Discharge – 6 months						
	$ECCO_2R$ (*n* = 202)			Ventilation alone (*n* = 210)			
Service	Obs	*N* (%)	Mean (95% CI)	Obs	*N* (%)	Mean (95% CI)	Mean difference (95% CI)
GP contact							
Face-to-face	149	64 (43.0)	1.44 (1.07 to 1.80)	150	63 (42.0)	1.66 (0.98 to 2.33)	−0.22 (−0.99 to 0.55)
Telephone	149	39 (26.2)	0.67 (0.44 to 0.91)	150	37 (24.7)	0.73 (0.46 to 1.01)	−0.06 (−0.42 to 0.30)
Home	149	15 (10.1)	0.18 (0.07 to 0.30)	150	21 (14.0)	0.45 (0.22 to 0.67)	−0.27 (−0.52 to −0.01)
Out of hours	149	6 (4.0)	0.05 (0.00 to 0.10)	150	9 (6.0)	0.09 (0.02 to 0.17)	−0.04 (−0.13 to 0.05)
GP nurse contact							
Face to face	149	49 (32.9)	1.00 (0.49 to 1.51)	150	33 (22.0)	1.13 (0.40 to 1.85)	−0.13 (−1.01 to 0.75)
Telephone	149	9 (6.0)	0.20 (−0.02 to 0.43)	150	11 (7.3)	0.19 (0.06 to 0.31)	0.01 (−0.24 to 0.27)
District nurse	149	25 (16.8)	1.68 (0.77 to 2.60)	150	31 (20.7)	3.17 (0.98 to 5.36)	−1.49 (−3.86 to 0.89)
Specialist nurse	149	18 (12.1)	0.60 (0.08 to 1.12)	150	21 (14.0)	0.48 (0.21 to 0.75)	0.12 (−0.46 to 0.70)
Social worker	149	9 (6.1)	0.25 (−0.03 to 0.53)	150	6 (4.0)	0.25 (−0.07 to 0.57)	0.00 (−0.42 to 0.42)
NHS physiotherapist	149	30 (20.1)	1.21 (0.52 to 1.91)	150	30 (20.0)	0.85 (0.47 to 1.22)	0.37 (−0.41 to 1.15)
Occupational therapist	149	23 (15.4)	0.52 (0.21 to 0.84)	150	25 (16.7)	1.28 (−0.53 to 3.10)	−0.76 (−2.60 to 1.08)
Dietitian	149	15 (10.1)	0.18 (0.08 to 0.28)	150	14 (9.3)	0.28 (0.02 to 0.54)	−0.10 (−0.38 to 0.18)
Counselling/therapy	149	11 (7.4)	0.36 (0.03 to 0.68)	150	10 (6.7)	1.22 (−0.60 to 3.05)	−0.87 (−2.72 to 0.98)
Speech and language therapy	149	3 (2.0)	0.03 (−0.00 to 0.07)	150	0 (0)	0 (0)	0.03 (−0.01 to 0.07)
NHS carer	149	11 (7.4)	4.39 (0.34 to 8.44)	150	7 (4.7)	7.04 (0.90 to 13.18)	−2.65 (−9.98 to 4.68)

continued

TABLE 7 Health resource use from hospital discharge to 6 months by treatment group (observed cases, without imputation of missing data) (*continued*)

	Discharge – 6 months						
	$ECCO_2R$ (*n* = 202)			Ventilation alone (*n* = 210)			
Service	Obs	*N* (%)	Mean (95% CI)	Obs	*N* (%)	Mean (95% CI)	Mean difference (95% CI)
Emergency department attendance							
Attendance, not admitted	149	11 (7.4)	0.13 (0.06 to 0.21)	150	13 (8.7)	0.13 (0.06 to 0.20)	0.01 (–0.09 to 0.11)
Attendance, admitted	149	16 (10.7)	0.15 (0.08 to 0.22)	150	11 (7.3)	0.13 (0.05 to 0.22)	0.01 (–0.10 to 0.13)
Ambulance	149	27 (18.1)	0.28 (0.17 to 0.39)	150	24 (16.0)	0.26 (0.15 to 0.37)	0.02 (-0.14, 0.18)
Hospital outpatient appointment	149	65 (43.6)	2.31 (1.53 to 3.10)	150	60 (40.0)	1.66 (1.11 to 2.21)	0.65 (–0.30 to 1.61)
Hospital admission	149	26 (17.5)	0.60 (0.50 to 0.71)	150	17 (11.3)	0.57 (0.47 to 0.66)	0.04 (–0.11 to 0.18)
Hospital days	149	–	2.87 (1.45 to 4.30)	150		2.14 (0.47 to 0.66)	0.73 (–1.26 to 2.71)
Oxygen therapy	149	2 (1.3)	–	150	2 (1.3)	–	

CI, confidence interval; *N* (%), number of participants using the service; *n*, number randomised; Obs, observed number of cases.

TABLE 8 Health resource use from 6 to 12 months by treatment group (observed cases, without imputation of missing data)

	6–12 months						
	ECCO$_2$R (*n* = 202)			Ventilation alone (*n* = 210)			
Service	Obs	*N* (%)	Mean (95% CI)	Obs	*N* (%)	Mean (95% CI)	Mean difference (95% CI)
GP contact							
Face-to-face	154	48 (31.2)	1.00 (0.65 to 1.35)	154	52 (33.8)	1.27 (0.88 to 1.66)	−0.27 (−0.79 to 0.25)
Telephone	154	29 (18.8)	0.73 (0.39 to 1.08)	154	34 (22.1)	0.72 (0.34 to 1.10)	0.01 (−0.50 to 0.53)
Home	154	8 (5.2)	0.14 (0.01 to 0.26)	154	10 (6.5)	0.26 (−0.01 to 0.53)	−0.12 (−0.42 to 0.17)
Out of hours	154	6 (3.9)	0.06 (0.01 to 0.11)	154	4 (2.6)	0.03 (−0.00 to 0.07)	0.03 (−0.04 to 0.09)
GP nurse contact							
Face to face	154	42 (27.3)	0.79 (0.41 to 1.16)	154	36 (23.4)	1.10 (0.50 to 1.70)	−0.31 (−1.01 to 0.40)
Telephone	154	8 (5.2)	0.10 (0.02 to 0.19)	154	12 (7.8)	0.17 (0.06 to 0.28)	−0.06 (−0.21 to 0.08)
District nurse	154	8 (5.2)	0.26 (−0.03 to 0.55)	154	6 (3.9)	0.19 (−0.00 to 0.38)	0.07 (−0.27 to 0.42)
Specialist nurse	154	17 (11.0)	0.47 (0.18 to 0.77)	154	15 (9.7)	0.22 (0.09 to 0.35)	0.25 (−0.07 to 0.57)
Social worker	154	5 (3.3)	0.09 (−0.00 to 0.19)	154	2 (1.3)	0.02 (−0.01 to 0.05)	0.07 (−0.03 to 0.17)
NHS Physiotherapist	154	20 (13.0)	0.82 (0.34 to 1.30)	154	14 (9.01)	0.52 (0.12 to 0.92)	0.30 (−0.32 to 0.92)
Occupational therapist	154	12 (7.8)	0.22 (0.09 to 0.36)	154	10 (6.5)	0.16 (0.04 to 0.29)	0.06 (−0.13 to 0.24)
Dietitian	154	14 (9.1)	0.19 (0.08 to 0.31)	154	8 (5.2)	0.15 (0.01 to 0.29)	0.05 (−0.14 to 0.23)
Counselling/therapy	154	10 (6.5)	0.33 (0.10 to 0.56)	154	6 (3.9)	0.18 (−0.01 to 0.36)	0.16 (−0.14 to 0.45)
Speech and language therapy	154	0 (0)	0 (0)	154	0 (0)	0 (0)	0 (0)
NHS carer	154	3 (2.0)	2.97 (−2.08 to 8.01)	154	2 (1.3)	1.61 (−1.56 to 4.77)	1.36 (−4.56 to 7.27)

continued

TABLE 8 Health resource use from 6 to 12 months by treatment group (observed cases, without imputation of missing data) (*continued*)

	6–12 months						
	ECCO$_2$R (*n* = 202)			Ventilation alone (*n* = 210)			
Service	Obs	*N* (%)	Mean (95% CI)	Obs	*N* (%)	Mean (95% CI)	Mean difference (95% CI)
Emergency department attendance							
Attendance, not admitted	154	10 (6.5)	0.09 (0.03 to 0.15)	154	7 (4.6)	0.05 (0.01 to 0.09)	0.04 (–0.03 to 0.10)
Attendance, admitted	154	15 (9.8)	0.16 (0.07 to 0.25)	154	9 (5.8)	0.10 (0.03 to 0.16)	0.06 (–0.05 to 0.17)
Ambulance	154	25 (16.2)	0.25 (0.15 to 0.36)	154	16 (10.4)	0.15 (0.07 to 0.23)	0.10 (–0.03 to 0.24)
Hospital outpatient appointment	154	54 (35.0)	2.44 (0.95 to 3.93)	154	46 (29.9)	1.37 (0.86 to 1.88)	1.07 (–0.50 to 2.64)
Hospital admission	154	20 (13.0)	0.53 (0.41 to 0.64)	154	11 (7.1)	0.47 (0.39 to 0.56)	0.05 (–0.09 to 0.20)
Hospital days	154	–	1.96 (0.62 to 3.30)	154	–	0.49 (0.06 to 0.92)	1.47 (0.07 to 2.88)
Oxygen therapy	154	3 (2.0)	–	154	2 (1.3)	–	–

Obs, observed number of cases.

TABLE 9 REST investigators

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
Temi	Adedoyin	Northwick Park Hospital	Research Co-ordinator
Kayode	Adeniji	Queen Alexandra Hospital	Principal Investigator
Caroline	Aherne	Royal Blackburn Hospital	Research Nurse
Gopal	Anand Iyer	Royal Liverpool Hospital	Coinvestigator
Prematie	Andreou	Leicester Royal Infirmary	Research Nurse
Gillian	Andrew	Edinburgh Royal Infirmary	Research Nurse
Ian	Angus	Royal Oldham Hospital	Research Nurse
Gill	Arbane	St Thomas's Hospital	Research Service Manager
Pauline	Austin	Ninewells Hospital	Coinvestigator
Karen	Austin	Worcester Hospital	Research Nurse
Georg	Auzinger	King's College London	Principal Investigator
Jonathan	Ball	St George's Hospital	Coinvestigator
Dorota	Banach	Charing Cross and Hammersmith	Research Nurse
Jonathan	Bannard-Smith	Manchester Royal Infirmary	Principal Investigator
Leona	Bannon	Royal Hospitals	Research Nurse
Lucy	Barclay	Edinburgh Royal Infirmary	Research Nurse
Helena	Barcraft-Barnes	Poole Hospital	Research Nurse
Richard	Beale	St Thomas's Hospital	Coinvestigator
Sarah	Bean	Royal Cornwall Hospital	Research Nurse
Andrew	Bentley	Wythenshawe Hospital	Principal Investigator
Georgia	Bercades	University College Hospital	Research Nurse
Colin	Bergin	Birmingham Queen Elizabeth Hospital	Research Nurse
Sian	Bhardwaj	Worcester Hospital	Principal Investigator
Colin	Bigham	Derriford Hospital	Principal Investigator
Isobel	Birkinshaw	York Teaching Hospital	Research Nurse
Aneta	Bociek	St Thomas's Hospital	Research Nurse
Andrew	Bodenham	Leeds General Hospital	Coinvestigator
Malcolm G	Booth	Glasgow Royal Infirmary	Coinvestigator
Christine	Bowyer	Wythenshawe Hospital	Research Nurse
David A	Brealey	University College Hospital	Coinvestigator
Stephen	Brett	Charing Cross and Hammersmith	Principal Investigator
Jennifer	Brooks	University of Wales Hospital	Research Nurse
Karen	Burt	Royal Cornwall Hospital	Research Nurse
Louise	Cabrelli	Ninewells Hospital	Research Nurse
Leilani	Cabreros	Charing Cross and Hammersmith	Research Nurse

continued

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
Hazel	Cahill	York Teaching Hospital	Research Nurse
Aidan	Campbell	Altnagelvin Hospital	Coinvestigator
Luigi	Camporota	St Thomas's Hospital	Principal Investigator
Sara	Campos	St Thomas's Hospital	Research Nurse
Julie	Camsooksai	Poole Hospital	Senior Research Nurse
Ronald	Carrera	Birmingham Queen Elizabeth Hospital	Research Nurse
Joseph	Carter	York Teaching Hospital	Principal Investigator
Jaime	Carungcong	Chelsea and Westminster	Research Nurse
Anelise	Catelan-Zborowski	Royal Brompton Hospital	Research Nurse
Susanne	Cathcart	Glasgow Royal Infirmary	Research Nurse
Shreekant	Champanerkar	Royal Gwent Hospital	Coinvestigator
Matthew	Charlton	Leicester Royal Infirmary	Coinvestigator
Shiney	Cherian	Royal Gwent Hospital	Research Nurse
Linsey	Christie	Chelsea and Westminster	Coinvestigator
Srikanth	Chukkambotla	Royal Blackburn Hospital	Principal Investigator
Amy	Clark	Birmingham Queen Elizabeth Hospital	Research Nurse
Sarah	Clark	Edinburgh Royal Infirmary	Research Nurse
Richard	Clark	Manchester Royal Infirmary	Research Nurse
Ian	Clement	Royal Victoria Infirmary	Principal Investigator
Eve	Cocks	University of Wales Hospital	Research Nurse
Stephen	Cole	Ninewells Hospital	Principal Investigator
Sonia	Cole	Sandwell General Hospital	Research Nurse
Jade	Cole	University of Wales Hospital	Research Nurse
Nick	Coleman	Royal Stoke Hospital	Coinvestigator
Emma	Connaughton	Manchester Royal Infirmary	Research Nurse
Andrew	Conway Morris	Addenbrookes Hospital	Coinvestigator
Lauren	Cooper	Birmingham Queen Elizabeth Hospital	Trial Co-ordinator
Ian	Cooper	Royal Oldham Hospital	Research Nurse
Carolyn	Corbett	Royal Oldham Hospital	Research Nurse
Sarah	Cornell	Sunderland Royal Hospital	Research Nurse
Carmen	Correia	Royal London Hospital	Research Nurse
Victoria	Cottam	New Cross Hospital	Research Nurse
Keith	Couper	Birmingham Heartlands Hospital	Research Nurse
Laura	Creighton	Royal Hospitals	Research Nurse
Maryam	Crews	Royal Liverpool Hospital	Coinvestigator
Neil	Crooks	Birmingham Heartlands Hospital	Coinvestigator

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
Jacqueline	Curtin	University of Wales Hospital	Research Nurse
Zoe	Daly	Queen Alexandra Hospital	Research Nurse
Alan	Davidson	Glasgow Queen Elizabeth	Coinvestigator
Rhys	Davies	University of Wales Hospital	Research Nurse
Michelle	Davies	University of Wales Hospital	Research Nurse
Christopher	Day	Royal Devon and Exeter Hospital	Principal Investigator
Mike	Dean	Northwick Park Hospital	Principal Investigator
Ged	Dempsey	Aintree Hospital	Principal Investigator
Anna	Dennis	Birmingham Heartlands Hospital	Coinvestigator
Susan	Dermody	Royal Oldham Hospital	Research Nurse
Liesl	Despy	Birmingham Queen Elizabeth Hospital	Research Nurse
Murugesh	Devaramani	Manchester Royal Infirmary	Research Nurse
Patricia	Doble	Musgrove Park Hospital	Research Nurse
Robert	Docking	Glasgow Queen Elizabeth	Coinvestigator
Adrian	Donnelly	Altnagelvin Hospital	Coinvestigator
Natalie	Dooley	Birmingham Queen Elizabeth Hospital	Research Nurse
Natalie	Dormand	Royal Brompton Hospital	Research Manager
Andrew	Drummond	Royal Oldham Hospital	Coinvestigator
Mark JG	Dunn	Edinburgh Royal Infirmary	Coinvestigator
Leigh	Dunn	Royal Victoria Infirmary	Research Nurse
Christine	Eastgate	Royal Free Hospital	Research Nurse
Karen	Ellis	Birmingham Queen Elizabeth Hospital	Research Nurse
Sarah	Farnell	St George's Hospital	Research Nurse
Helen	Farrah	St George's Hospital	Research Nurse
Emma	Fellows	Birmingham Queen Elizabeth Hospital	Research Nurse
Timothy	Felton	Wythenshawe Hospital	Coinvestigator
Helder	Filipe	Royal Free Hospital	Research Nurse
Clare	Finney	King's College London	Research Nurse
Simon	Finney	Royal Brompton Hospital	Coinvestigator
Jillian	Fitchett	Royal Blackburn Hospital	Research Nurse
Brian	Gammon	Sandwell General Hospital	Research Nurse
Saibal	Ganguly	New Cross Hospital	Coinvestigator
Minerva	Gellamucho	Royal Stoke Hospital	Research Nurse
Susan	Gibson	Ninewells Hospital	Research Nurse
Charles	Gibson	Royal Devon and Exeter Hospital	Coinvestigator

continued

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
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Michael A	Gillies	Edinburgh Royal Infirmary	Principal Investigator
Stuart	Gillon	Glasgow Queen Elizabeth	Coinvestigator
Shameer	Gopal	New Cross Hospital	Principal Investigator
Anthony	Gordon	Imperial College	Coinvestigator
Stephanie	Goundry	Birmingham Queen Elizabeth Hospital	Research Nurse
Lia	Grainger	York Teaching Hospital	Research Nurse
Neus	Grau Novellas	St Thomas's Hospital	Research Nurse
Joanne	Gresty	Birmingham Heartlands Hospital	Research Nurse
Mark	Griffiths	St Bartholomews	Coinvestigator
Jamie	Gross	Northwick Park Hospital	Coinvestigator
Una	Gunter	Royal Gwent Hospital	Research Nurse
Karen	Hallett	Royal Oldham Hospital	Research Nurse
Samantha	Harkett	Birmingham Queen Elizabeth Hospital	Research Nurse
Donna	Harrison-Briggs	Royal Blackburn Hospital	Research Nurse
Louise	Hartley	Glasgow Queen Elizabeth	Coinvestigator
Ingrid	Hass	University College Hospital	Research Nurse
Noel	Hemmings	Altnagelvin Hospital	Coinvestigator
Steven	Henderson	Glasgow Queen Elizabeth	Research Nurse
Helen	Hill	University of Wales Hospital	Research Nurse
Gemma	Hodkinson	Royal Gwent Hospital	Research Nurse
Kate	Howard	York Teaching Hospital	Research Nurse
Clare	Howcroft	St James Hospital	Research Nurse
Ying	Hu	Royal London Hospital	Research Nurse
Jonathan	Hulme	Sandwell General Hospital	Principal Investigator
Tariq	Husain	Northwick Park Hospital	Coinvestigator
Joanne	Hutter	Musgrove Park Hospital	Research Nurse
Dorothy	Ilano	University College Hospital	Staff Nurse
Richard	Innes	Musgrove Park Hospital	Principal Investigator
Nicola	Jacques	Royal Berkshire Hospital	Research Lead Nurse
Sarah	James	Royal Free Hospital	Research Nurse
Sarah	Jenkins	Poole Hospital	Research Nurse
Paul	Johnston	Antrim Area Hospital	Principal Investigator
Brian	Johnston	Royal Liverpool Hospital	Coinvestigator
Colette	Jones-Criddle	Aintree Hospital	Research Sister
Santhana	Kannan	Sandwell General Hospital	Coinvestigator

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
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Andrea	Kelly	St Thomas's Hospital	Research Nurse
Sophie	Kennedy-Hay	Glasgow Queen Elizabeth	Research Nurse
Liana	Lankester	Derriford Hospital	Research Nurse
Susannah	Leaver	St George's Hospital	Principal Investigator
Stephane	Ledot	Royal Brompton Hospital	Principal Investigator
Rosario	Lim	St Thomas's Hospital	Research Nurse
Lucie	Linhartova	Birmingham Heartlands Hospital	Coinvestigator
Fei	Long	Northwick Park Hospital	Research Nurse
Niall S	MacCallum	University College Hospital	Principal Investigator
Sarah	MacGill	Royal Berkshire Hospital	Research Nurse
Andrew	Mackay	Glasgow Queen Elizabeth	Coinvestigator
Sarah	Maclean	Ninewells Hospital	Coinvestigator
Amber	Markham	Sandwell General Hospital	Matron
Daniel	Martin	Royal Free Hospital	Principal Investigator
Tim	Martin	Royal London Hospital	Research Nurse
Tracy	Mason	Birmingham Queen Elizabeth Hospital	Research Nurse
Nick	Mason	Royal Gwent Hospital	Coinvestigator
Justine	McCann	Royal Hospitals	Research Nurse
Corrienne	McCulloch	Edinburgh Royal Infirmary	Research Nurse
Christopher	McGhee	Birmingham Queen Elizabeth Hospital	Research Nurse
Loren	McGinley-Keag	Royal Hospitals	Research Nurse
Michael	McLaughlin	Glasgow Royal Infirmary	Coinvestigator
Lia	McNamee	Royal Hospitals	Research Physician Associate
Margaret	McNeil	Royal Free Hospital	Research Nurse
Laura	Mee	Birmingham Queen Elizabeth Hospital	Research Administrator
Claire	Mellis	King's College London	Research Nurse
Teresa	Melody	Birmingham Heartlands Hospital	Research Manager
Jeanette	Mills	Royal Hospitals	Research Nurse
Esther	Molina	Leicester Royal Infirmary	Research Nurse
Matt PG	Morgan	University of Wales Hospital	Principal Investigator
Mushiya	Mpelembue	Northwick Park Hospital	Research Co-ordinator
Stephanie	Muldoon	Birmingham Queen Elizabeth Hospital	Research Nurse
Sheila	Munt	Royal Oldham Hospital	Research Nurse
Alistair	Nichol	University College Dublin	Collaborator

continued

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
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Christopher	Nutt	Royal Hospitals	Coinvestigator
Sinead	O'Kane	Altnagelvin Hospital	Research Nurse
Aisling	O'Neill	Royal Hospitals	Research Nurse
Valerie	Page	Watford General Hospital	Principal Investigator
Elankumaran	Paramasivam	St James Hospital	Principal Investigator
Dhruv	Parekh	Birmingham Queen Elizabeth Hospital	Coinvestigator
Sarah	Patch	Poole Hospital	Research Nurse
Sameer	Patel	King's College London	Coinvestigator
Lia	Paton	Glasgow Royal Infirmary	Coinvestigator
Gavin	Perkins	Birmingham Heartlands Hospital	Principal Investigator
Manuel	Pinto	Royal Free Hospital	Research Nurse
David	Pogson	Queen Alexandra Hospital	Coinvestigator
Petra	Polgarova	Addenbrookes Hospital	Research Nurse
Jagtar	Pooni	New Cross Hospital	Coinvestigator
Martin	Pope	Birmingham Queen Elizabeth Hospital	Clinical Trials Assistant
Grant C	Price	Edinburgh Royal Infirmary	Coinvestigator
Jashmin	Priya Maria	Manchester Royal Infirmary	Research Nurse
Lynda	Purdy	Royal Hospitals	Research Nurse
Alex	Puxty	Glasgow Royal Infirmary	Principal Investigator
John	Rae	Ninewells Hospital	Coinvestigator
Mark	Raper	University of Wales Hospital	Coinvestigator
Henrik	Reschreiter	Poole Hospital	Principal Investigator
Steve	Rose	Queen Alexandra Hospital	Research Nurse
Anthony	Rostron	Sunderland Royal Hospital	Coinvestigator
Alistair	Roy	Sunderland Royal Hospital	Principal Investigator
Christine	Ryan	St George's Hospital	Research Nurse
Jung	Ryu	University College Hospital	Study Co-ordinator
Kiran	Salaunkey	Papworth Hospital	Principal Investigator
Julia	Sampson	Birmingham Heartlands Hospital	Research Nurse
Vivian	Sathianathan	Northwick Park Hospital	Coinvestigator
Lorraine	Scaife	Royal Devon and Exeter Hospital	Senior Research Nurse
Simon WM	Scott	Leicester Royal Infirmary	Principal Investigator
Timothy E	Scott	Royal Stoke Hospital	Principal Investigator
Sumant	Shanbhag	Manor Hospital	Principal Investigator
David	Shaw	Royal Liverpool Hospital	Research Nurse

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
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Suveer	Singh	Chelsea and Westminster	Principal Investigator
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Hazel	Smith	Birmingham Queen Elizabeth Hospital	Research Paramedic
John	Smith	King's College London	Senior Research Nurse
Jayne	Smith	Poole Hospital	Senior Research Facilitator
Deborah	Smyth	University College Hospital	Senior Nurse
Catherine	Snelson	Birmingham Queen Elizabeth Hospital	Coinvestigator
Michael	Spivey	Royal Cornwall Hospital	Principal Investigator
Elaine	Spruce	Birmingham Queen Elizabeth Hospital	Research Nurse
Charlotte	Summers	Addenbrookes Hospital	Principal Investigator
Peter	Sutton	Birmingham Heartlands Hospital	Research Nurse
Tamas	Szakmany	Royal Gwent Hospital	Principal Investigator
Nicholas	Talbot	Birmingham Queen Elizabeth Hospital	Coinvestigator
Maie	Templeton	Charing Cross and Hammersmith	Research Nurse
Jessica	Thrush	Worcester Hospital	Research Nurse
Redmond	Tully	Royal Oldham Hospital	Principal Investigator
William	Tunnicliffe	Birmingham Queen Elizabeth Hospital	Principal Investigator
Ian	Turner-Bone	Aintree Hospital	Research Nurse
Tonny	Veenith	Birmingham Queen Elizabeth Hospital	Coinvestigator
Alan	Vuylsteke	Papworth Hospital	Coinvestigator
Andrew	Walden	Royal Berkshire Hospital	Principal Investigator
Jonathan	Walker	Royal Liverpool Hospital	Coinvestigator
Kathryn	Ward	Royal Hospitals	Research Nurse
Tim	Walsh	Edinburgh Royal Infirmary	Coinvestigator
Victoria	Waugh	Royal Liverpool Hospital	Research Nurse
Colin	Wells	Derriford Hospital	Research Nurse
Ingeborg	Welters	Royal Liverpool Hospital	Principal Investigator
Tony	Whitehouse	Birmingham Queen Elizabeth Hospital	Coinvestigator
Arlo	Whitehouse	Birmingham Queen Elizabeth Hospital	Research Nurse
Christopher	Whitton	University of Wales Hospital	Research Nurse
Elizabeth	Wilby	St James Hospital	Research Nurse
Danielle	Wilcox	York Teaching Hospital	Research Nurse
Laura	Wilding	Aintree Hospital	Research Nurse
James	Williams	Royal Gwent Hospital	Coinvestigator

continued

TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
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Sarah	Winnard	Royal Oldham Hospital	Research Nurse
Lindsey	Woods	Sunderland Royal Hospital	Research Nurse
Chris	Wright	Glasgow Queen Elizabeth	Coinvestigator
Neil H	Young	Edinburgh Royal Infirmary	Coinvestigator
Xiaobei	Zhao	Watford General Hospital	Research Nurse
Parjam	Zolfaghari	Royal London Hospital	Principal Investigator

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The Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal Compared With Conventional Lung Protective Ventilation on Cardiac Function

McGuigan PJ, Bowcock EM, Barrett NA, Blackwood B, Boyle AJ, Cadamy AJ, *et al*. The Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal Compared With Conventional Lung Protective Ventilation on Cardiac Function. *Crit Care Explor* 2024;**6**(1):e1028. https://doi.org/10.1097/CCE.0000000000001028

DOI

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Determinants of Effect of Extracorporeal CO_2 Removal in Hypoxemic Respiratory Failure

Dianti J, McNamee JJ, Slutsky AS, Fan E, Ferguson ND, McAuley DF, Goligher EC. Determinants of Effect of Extracorporeal CO_2 Removal in Hypoxemic Respiratory Failure. *NEJM Evid* 2023;**2**(5):EVIDoa2200295. https://doi.org/10.1056/EVIDoa2200295

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