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

Ashley Agus[1*], James J. McNamee[2], Colette Jackson[1] and Danny F. McAuley[2,3]

[1]Northern Ireland Clinical Trials Unit, Belfast, UK
[2]Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, UK
[3]Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Science, Queen's University of Belfast, Belfast, UK

[*]Corresponding author

Disclosure of interests of authors

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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

Ashley Agus[1*] James J. McNamee[2] Colette Jackson[1] and Danny F. McAuley[2,3]

[1]Northern Ireland Clinical Trials Unit, Belfast, UK
[2]Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, UK
[3]Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Science, Queen's University of Belfast, Belfast, UK

[*]Corresponding author ashley.agus@nictu.hscni.net

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).

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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

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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.

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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.

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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.

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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[a,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.

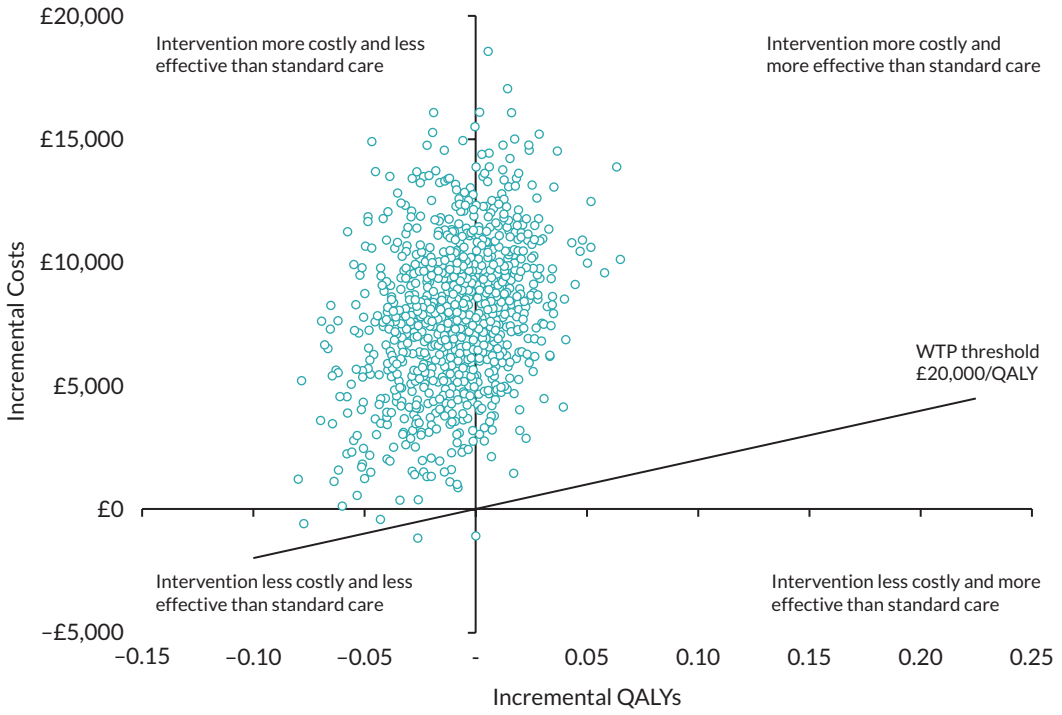

FIGURE 1 Cost-effectiveness plane for the base-case cost-utility analysis showing 1000 bootstrapped replications of incremental mean costs and QALYs and the WTP threshold of £20,000/QALY.

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$_2$R 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$_2$R 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$_2$R 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$_2$R 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.

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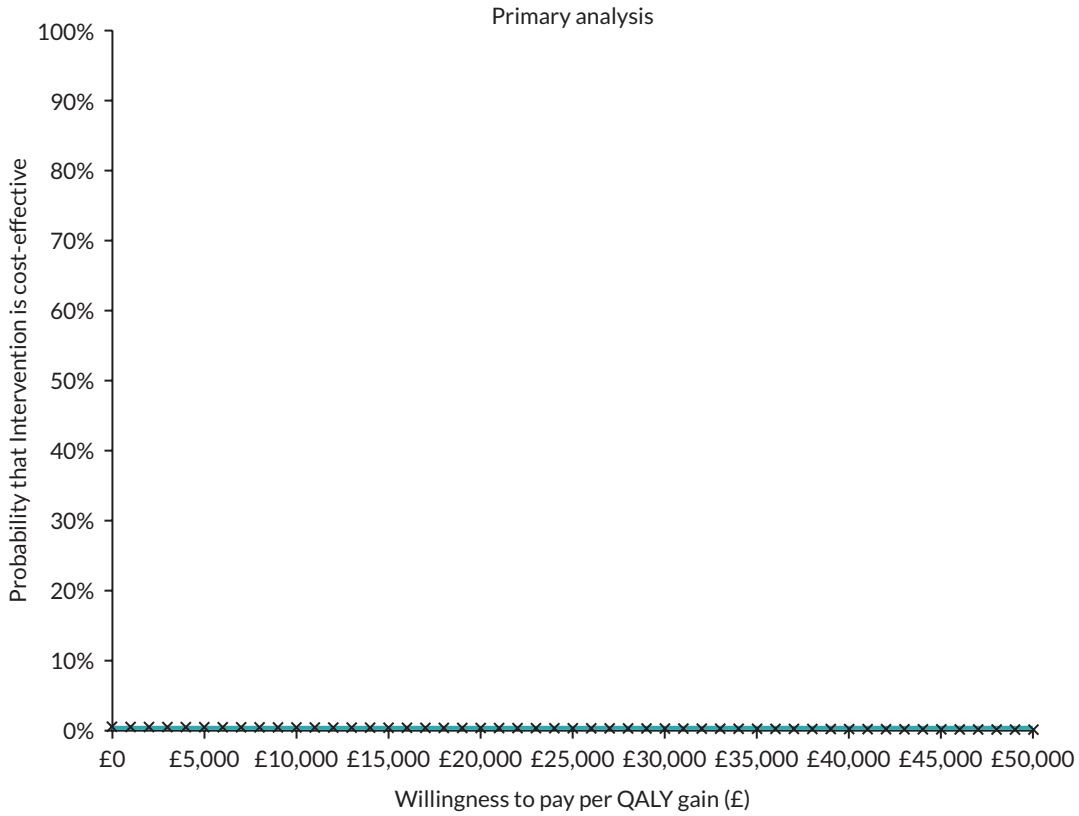

FIGURE 2 Cost-effectiveness acceptability curve showing the probability of intervention being cost-effective compared to standard care (base-case analysis).

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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This article

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This article reports on one component of the research award Extracorporeal carbon dioxide removal compared to ventilation alone in patients with acute hypoxaemic respiratory failure: cost-utility analysis of the REST RCT. For more information about this research please view the award page [https://www.fundingawards.nihr.ac.uk/award/13/143/02]

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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

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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

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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						
	$ECCO_2R$ (*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	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)

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

	6–12 months						
	$ECCO_2R$ (*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	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

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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

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TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
Lynn	Gilfeather	Altnagelvin Hospital	Principal Investigator
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
Parminder	Kaur Bhuie	Royal Berkshire Hospital	Research Nurse
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

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TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
Nazril	Nordin	Watford General Hospital	Coinvestigator
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
Malcolm	Sim	Glasgow Queen Elizabeth	Principal Investigator
Suveer	Singh	Chelsea and Westminster	Principal Investigator
Andrew	Smallwood	New Cross Hospital	Research Nurse
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

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TABLE 9 REST investigators (*continued*)

First name and middle initial(s)	Last name	Institution	Role or contribution, for example, chair, principal investigator
Karen	Williams	Royal Liverpool Hospital	Research Nurse
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