Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

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Summary

Background Severe acute respiratory failure in adults causes high mortality despite improvements in ventilation techniques and other treatments (eg, steroids, prone positioning, bronchoscopy, and inhaled nitric oxide). We aimed to delineate the safety, clinical efficacy, and cost-effectiveness of extracorporeal membrane oxygenation (ECMO) compared with conventional ventilation support.

Methods In this UK-based multicentre trial, we used an independent central randomisation service to randomly assign 180 adults in a 1:1 ratio to receive continued conventional management or referral to consideration for treatment by ECMO. Eligible patients were aged 18–65 years and had severe (Murray score >3·0 or pH <7·20) but potentially reversible respiratory failure. Exclusion criteria were: high pressure (>30 cm H_2O of peak inspiratory pressure) or high FiO_2 (>0·8) ventilation for more than 7 days; intracranial bleeding; any other contraindication to limited heparinisation; or any contraindication to continuation of active treatment. The primary outcome was death or severe disability at 6 months after randomisation or before discharge from hospital. Primary analysis was by intention to treat. Only researchers who did the 6-month follow-up were masked to treatment assignment. Data about resource use and economic outcomes (quality-adjusted life-years) were collected. Studies of the key cost generating events were undertaken, and we did analyses of cost-utility at 6 months after randomisation and modelled lifetime cost-utility. This study is registered, number ISRCTN47279827.

Findings 766 patients were screened; 180 were enrolled and randomly allocated to consideration for treatment by ECMO (n=90 patients) or to receive conventional management (n=90). 68 (75%) patients actually received ECMO; 63% (57/90) of patients allocated to consideration for treatment by ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management (relative risk 0·69; 95% CI 0·05–0·97, p=0·03). Referral to consideration for treatment by ECMO treatment led to a gain of 0·03 quality-adjusted life-years (QALYs) at 6-month follow-up. A lifetime model predicted the cost per QALY of ECMO to be £19 252 (95% CI 7622–59 200) at a discount rate of 3·5%.

Interpretation We recommend transferring of adult patients with severe but potentially reversible respiratory failure, whose Murray score exceeds 3·0 or who have a pH of less than 7·20 on optimum conventional management, to a centre with an ECMO-based management protocol to significantly improve survival without severe disability. This strategy is also likely to be cost effective in settings with similar services to those in the UK.

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Introduction

Despite advances in intensive care during the past 20 years, mortality and morbidity of patients with acute respiratory distress syndrome remains high; mortality for such patients is 34–58%.[1–6] Surviving patients could have clinically significant physical (respiratory and musculoskeletal) and neuropsychological (emotional and cognitive) disabilities.[3] Such patients need inpatient rehabilitation and hospital readmissions, leading to high financial burden on carers and health-care systems.[3]

Conventional management is by intermittent positive-pressure ventilation, which can cause very high airway pressures and oxygen concentrations. The combination of barotrauma, volutrauma, biotrauma, and toxic effects of oxygen exacerbates lung injury from the primary illness. An alternative treatment, extracorporeal membrane oxygenation (ECMO), uses cardiopulmonary bypass technology to provide gas exchange so that ventilator settings can be reduced, which provides time for treatment and recovery.

Two previous randomised controlled trials have assessed adult extracorporeal life support.[7,8] Neither of these studies has relevance to modern ECMO because the case selection, ventilation strategies, extracorporeal

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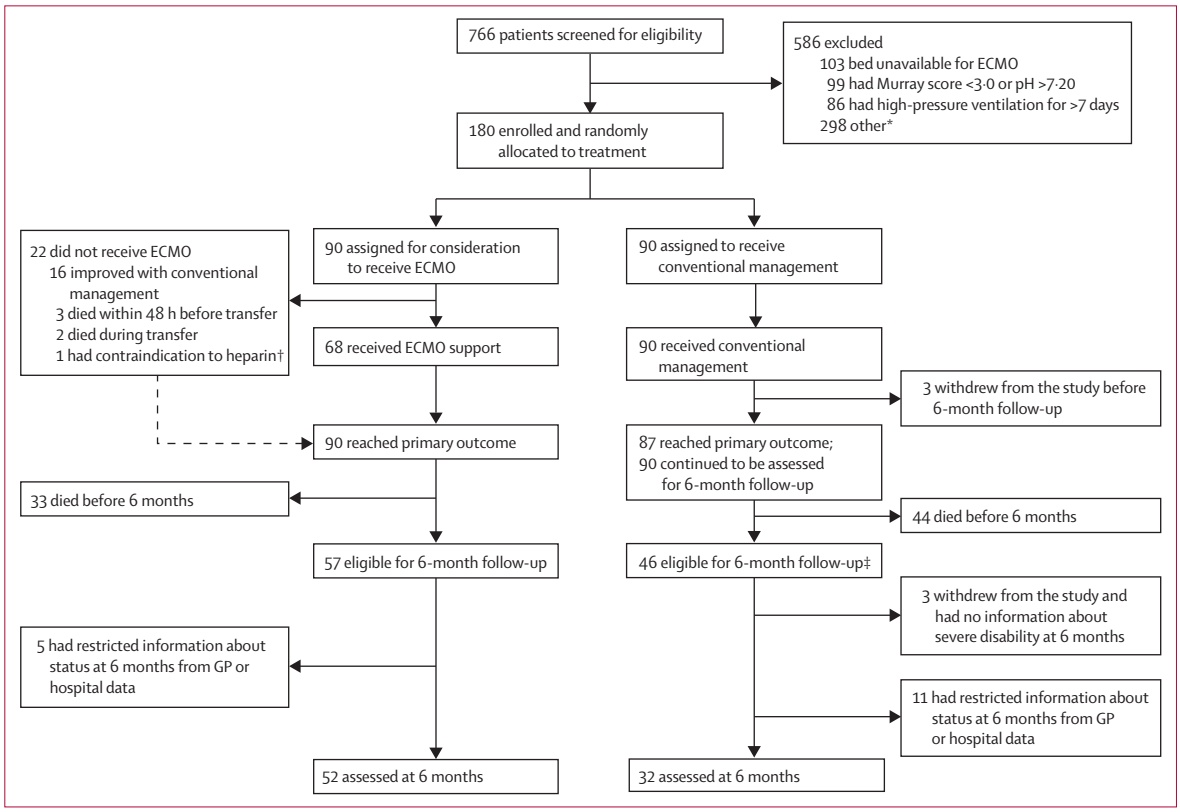

Figure 1: **Trial profile**
ECMO=extracorporeal membrane oxygenation. *81 were contraindicated to continue with treatment, 35 were only enquiries, 35 received advice on optimum conventional management, 33 refused assent, 31 had contraindications to limited heparinisation, 30 were younger than 18 years or older than 65 years, 28 had the treating clinician refuse enrolment, eight had an improving condition, seven had no relatives available to provide assent, four died before randomisation, three had intracranial bleeding, two were given advice on ECMO treatment, and one had had previous surgical treatment. †Patient needed amputation and therefore could not be heparinised. ‡Includes one patient with follow-up assessment at 6 months in hospital and who died after 6 months without leaving hospital.

circuit design, and disease management were completely different from modern protocols. Therefore observational studies provide the only relevant evidence. Case series of patients with severe respiratory failure report survival rates without ECMO of 18–44%[6,9] compared with up to 66% with ECMO (including full support of oxygenation and lung rest).[10–12] To further define the safety, clinical efficacy, and cost-effectiveness of ECMO, we did the rigorous randomised controlled trial CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) in combination with an economic evaluation from the perspective of the health-care provider, the UK National Health Service (NHS).

Methods

Participants

Patients were enrolled from three types of centre: the ECMO centre at Glenfield Hospital, Leicester, which treated all patients who were randomly allocated for consideration to receive ECMO; tertiary intensive care units (conventional treatment centres); and referral hospitals, which sent patients to the conventional treatment centres if they were randomly allocated to receive continued conventional management.[13] 103 hospitals obtained ethics committee approval to collaborate in the study of which 92 were conventional treatment centres and 11 were referral hospitals.

Patients were unconscious, intubated, and ventilated, and therefore were not able to give consent for inclusion in the study at randomisation. Relatives gave assent on every patient's behalf, and patients were later given the opportunity to withdraw from the study. The trial was approved by the Trent Multicentre Research Ethics Committee and relevant local research ethics committees for every paricipating centre.

Eligible patients were aged 18–65 years with severe but potentially reversible respiratory failure, and a Murray score[14] (from all four variables—PaO_2/FiO_2 ratio, positive end-expiratory pressure, lung compliance, and chest radiograph appearance—and FiO_2=1) of 3·0 or higher, or uncompensated hypercapnoea with a pH of less than 7·20 despite optimum conventional treatment. Reversibility was based on the clinical opinion of one of three duty ECMO consultants. The criteria for case selection have been previously discussed.[15] Patients were also considered for inclusion if the Murray score was 2·5 or

	ECMO group (n=90)*	Conventional management group (n=90)
Hospital of trial entry†		
Conventional treatment centre	73 (81%)	75 (83%)
Referral hospital	17 (19%)	15 (17%)
Men	51 (57%)	53 (59%)
Age†	39·9 (13·4)	40·4 (13·4)
18–30	25 (28%)	23 (26%)
31–45	29 (32%)	32 (36%)
46–65	36 (40%)	35 (39%)
Primary diagnosis†		
Pneumonia	56 (62%)	53 (59%)
Obstetric ARDS	0	0
Other ARDS	25 (28%)	26 (29%)
Trauma including surgery within 24 h	5 (6%)	7 (8%)
Other	4 (4%)‡	4 (4%)§
Number of organs failed†		
1–2 organs	62 (69%)	63 (70%)
≥3 organs	28 (31%)	27 (30%)
Duration of intermittent positive-pressure ventilation at entry (h)	35·0 (17·3–104·5)	37·0 (15·5–101·5)
0–48	46 (51%)	51 (57%)
49–168	36 (40%)	32 (36%)
>168	6 (7%)	7 (8%)
Missing data	2 (2%)	0
Duration of high-pressure ventilation or high FiO_2, or both (h)†	28·5 (17·0–69·3)	28·0 (12·0–88·0)
0–48	56 (62%)	59 (66%)
49–168	34 (38%)	31 (34%)
Disorder leading to study entry		
Hypoxia†	85 (94%)	87 (97%)
Murray score	3·5 (0·6)	3·4 (0·3)
PaO_2/FiO_2 (mm Hg^{-1})	75·9 (29·5)	75·0 (35·7)
Positive end-expiratory pressure (cm H_2O)	13·7 (9.6)	14·2 (9·4)
Lung compliance (mL/cm H_2O)	27·4 (12·2)	25·3 (8·0)
Chest radiograph (quadrants infiltrated)	3·5 (0·7)	3·7 (0·6)
Uncompensated hypercapnoea†	5 (6%)	3 (3%)
pH	7·1 (0·1)	7·1 (0·1)
APACHE II score¶	19·68 (6·3)	19·9 (6·1)
Missing data	33 (37%)	29 (32%)

Data are number (%), mean (SD), or median (IQR). ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. †Minimisation factor. ‡Including asthma, Weil's disease, dermatomyositis, and pancreatitis. §Including asthma, aspiration, asthma and bronchospasm, and acute milliary tuberculosis. ¶Based on 24 h after admission to intensive care, or up to trial entry if this is less than 24 h.

Table 1: **Demographic characteristics at baseline**

	ECMO group (n=90)*†	Conventional management group (n=90)	p value
Treatment by ECMO	68 (76%)	NA	NA
Transport to treatment centre	62 (69%)	NA	NA
Air (with or without ground transport)	24 (27%)	NA	NA
Ground	38 (42%)	NA	NA
Not transferred‡	6 (7%)	NA	NA
Time between randomisation and treatment (h)	6·1 (4·0–7 ·1)§	NA	NA
Duration of treatment (days)	9·0 (6·0–16·0)¶	NA	NA
Treatment by conventional management	22 (24%)	90 (100%)	NA
Transport to treatment centre	19 (21%)	11 (12%)‖	NA
Air (with or without ground transport)	5 (6%)	2 (2%)	NA
Ground	14 (1%)	9 (10%)	NA
Not transferred	3 (3%)	79 (88%)	NA
Duration of treatment (days)	10 (4·8–22·8)	11 (4·0–20·3)	NA
Treatment by other management			
Missing all data	2 (2%)	0	NA
High-frequency oscillation or jet ventilation	6 (7%)	13 (14%)	0·21
Nitric oxide	9 (10%)	6 (7%)	0·60
Prone position	32 (4%)	38 (42%)	0·58
Steroids	76 (84%)	58 (64%)	0·001
MARS	15 (17%)	0	<0·0001
Continuous venovenous haemofiltration	72 (80%)	76 (84%)	0·61
Treatment by low-volume low-pressure ventilation strategy at any time	84 (93%)	63 (70%)	<0·0001
Time under strategy (days)	23·9 (20·4)	15·0 (21·1)	<0·0001

Data are number (%), median (IQR), or mean (SD). ECMO=extracorporeal membrane oxygenation. NA=not applicable. IPPV=intermittent positive-pressure ventilation. MARS=molecular albumin recirculating system. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. †Three patients died within 48 h before transfer. ‡Patients already in the ECMO centre receiving conventional management. §Data for 66 patients, including one patient whose condition improved on arrival at the ECMO centre and so received conventional management, but deteriorated 10 days later and so ECMO was started. ¶Data for 67 patients, including three patients who had a second course of ECMO. ‖A further four patients were randomised to conventional management from referral hospitals, but were not transferred. Three of these patients died: one before transfer, one was not permitted to transfer by the family, and one was deemed too sick to move by the transport team. The remaining patients was deemed too sick to move by the transport team.

Table 2: **Actual management after randomisation**

higher, so that trial entry could be accelerated if the patient continued to dete riorate.

Patients were excluded if they had: been on high pressure (peak inspiratory pressure >30 cm H_2O) or high FiO_2 (>0·8) ventilation for more than 168 h (7 days); signs of intracranial bleeding; any other contraindication to limited heparinisation; or any contraindication to continuation of active treatment. Ventilation parameters were assessed on an hourly basis for high-pressure (peak airway pressure >30 cm H_2O) or high FiO_2 (>0·8) ventilation.

Study design

We designed CESAR to be a pragmatic trial, similar to the UK trial of neonatal ECMO[16,17] in which the best standard practice was compared with a protocol that included ECMO. For patients with severe, but potentially reversible, respiratory failure, the primary hypothesis was that an ECMO based protocol would increase survival without severe disability by 6 months after randomisation compared with conventional ventilation, and be cost effective from the perspective of the NHS and society. The protocols for the RCT and for the concurrent economic study have been published separately.[13,18]

	ECMO group (n=90)*	Conventional management group (n=90)	Relative risk (95% CI, p value)
Death or severe disability at 6 months	NA	NA	0·69 (0·05–0·97, 0·03)†
No	57 (63%)	41 (47%)‡	NA
Yes	33 (37%)	46 (53%)‡	NA
No information about severe disability	0	3 (3%)§	NA
Died at ≤6 months or before discharge	NA	NA	0·73 (0·52–1·03, 0·07)
No	57 (63%)	45 (50%)	NA
Yes	33 (37%)	45 (45%)	NA
Severe disability			
No	57 (63%)	41 (46%)	NA
Yes	0	1 (1%)	NA
Cause of death			
Respiratory failure	8 (9%)	24 (27%)	NA
Multiorgan failure	14 (16%)	15 (17%)	NA
Neurological disorder	4 (4%)	2 (2%)	NA
Cardiovascular disorder	1 (1%)	3 (3%)	NA
Related to ECMO	1 (1%)	0	NA
Other	1 (1%)	0	NA
Unknown	4 (4%)	1 (1%)	NA
Time between randomisation and death (days)	15 (3–41)	5 (2–14)	NA

Data are number (%) or median (IQR), unless otherwise indicated. ECMO=extracorporeal membrane oxygenation. NA=not applicable. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. †Based on 177 patients with known primary outcome. Assuming that the three patients in the conventional management group who had no information about disability had all been severely disabled, or had not been severely disabled, relative risk of the primary outcome would be 0·67 (95% CI 0·48–0·94, p=0·017), and 0·72 (0·51–1·01, p=0·051), respectively. ‡Percentage calculated with denominator of 87 patients to exclude those with no information about severe disability. §Patients had been discharged from hospital 1–3 months after randomisation, and were known to be alive at 6 months.

Table 3: **Death and severe disability**

The intensivist in the originating hospital contacted the advisory team at Glenfield Hospital to confirm eligibility and bed availability. The intensivist then discussed the trial with at least one of the patient's relatives, supplied written information to them, and asked them to provide informed assent on behalf of the patient. The adviser then telephoned the independent central randomisation service. Patients were randomly allocated by minimisation in a 1:1 ratio to conventional management by intermittent positive-pressure ventilation or high-frequency oscillatory ventilation, or both, or consideration for treatment by ECMO. Minimisation factors were type of centre; age; hours of high-pressure or high FiO_2 ventilation; presence of hypoxia or hypercarbia; diagnostic group; and number of organs failed. We did not stratify patients according to pulmonary and extrapulmonary acute respiratory distress syndrome because our previous experience of treating patients with ECMO indicated that this stratification did not have an effect on outcome, whereas the other minimisation criteria did affect outcome.[11] Masking of treating physicians, patients, or any other medical staff was not possible at this stage of treatment. An emergency inclusion protocol allowed entry from hospitals not registered with the study.[13]

Patients randomly allocated to receive conventional management were given the best critical care practice available in their conventional treatment centre. As a pragmatic trial, a specific management protocol was not mandated, but treatment centres were advised to follow a low-volume low-pressure ventilation strategy—ie, tidal volume of 4–8 mL/kg bodyweight,[19] and pressure plateau of less than 30 cm H_2O. Patients could not cross over to receive ECMO.

Patients randomly allocated to consideration for treatment by ECMO were transferred to Glenfield Hospital. If patients were haemodynamically stable, a standard acute respiratory distress syndrome treatment protocol was used, which comprised pressure-restricted mechanical ventilation at 30 cm H_2O, positive end-expiratory pressure titrated to optimum SaO_2, FiO_2 titrated to maintain SaO_2 at more than 90%, diuresis to dry weight, target packed cell volume of 40%, prone positioning, and full nutrition. If the patient did not respond to this protocol within 12 h (FiO_2>90% needed to maintain SaO_2>90%, respiratory or metabolic acidosis <7·2) or was haemodynamically unstable, they received cannulation and ECMO. Management on ECMO (including rest ventilator settings) was according to published institutional protocols.[11,13] All ECMO was done in the venovenous mode with percutaneous cannulation. Servo-controlled roller pumps (Stockert, Freiburg, Germany) and poly-methyl pentene oxygenators (Medos Medizintechink, Stolberg, Germany) were used. Ventilation was in pressure control mode with Siemens Servo 300 ventilators (Solma, Sweden); lung rest settings were peak inspiratory pressure 20–25, positive end-expiratory pressure 10–15, rate 10, and FiO_2 0·3. ECMO was continued until lung recovery, or until apparently irreversible multiorgan failure.

All inward transport was provided by the ECMO team, including transfer of patients from referral hospitals to conventional treatment centres. If the team decided that it was not safe to move the patient then they remained in the original unit until considered safe to transfer, recovered, or died. Patients were not transported while on ECMO.

Basic information was collected for all patients who were screened and considered for the trial. For patients who were enrolled and randomly allocated to treatment, we gathered data about demographic indicators; diagnoses that focused on the cause of acute respiratory distress syndrome; dates of hospitalisation, intubation, extubation, and discharge from intensive care and hospital; condition at discharge; major complications; and cause of death. Physiological data obtained at randomisation were ventilator settings, blood gases, haemodynamic status, and variables of the APACHE II score.[20] Murray lung injury score and ratio of PaO_2 to FiO_2 were calculated. After randomisation, we collected data from patients on conventional management about time course of treatment, complications, other methods of respiratory treatment (eg, nitric oxide,

steroids), primary and secondary outcomes, and compliance with the low-volume low-pressure ventilation strategy (pressure plateau or positive inspiratory pressure less than 30 cm H_2O). We collected these data for patients on ECMO, in addition to ECMO management information (cannulation, flow, pressure, device, and complications).

The primary outcome measure was death or severe disability at 6 months after randomisation (defined as death by 6 months or before discharge from hospital at any time to the end of data collection). Severe disability was defined as confinement to bed and inability to wash or dress alone; according to this definition, all patients were severely disabled at randomisation, but no patients were disabled before they became ill and entered the study. Secondary outcomes were duration of ventilation; use of high-frequency oscillation, or jet ventilation; use of nitric oxide; prone positioning; use of steroids; duration of stay in intensive care; and duration of hospital stay. For patients receiving ECMO only, secondary outcomes also included method of ECMO (venovenous or venoarterial), duration of ECMO, blood flow, and sweep flow. Health status at 6 months after randomisation was assessed from activities of daily living, quality of life, respiratory symptoms, cognitive psychological state, and lung function.

At the 6-month follow-up, testing was done in the patients' homes by trained researchers who were masked to treatment allocation. Patients and their relatives were instructed not to reveal which treatment had been used. A scarf was used to cover the neck, thereby masking cannulation status. Assessment was done by SF-36,[21] EuroQol-5 dimensions (EQ-5D),[22] St George's hospital respiratory questionnaire,[23] hospital anxiety and depression scale,[24] and mini-mental state examination,[25] and specific questions were asked about sleep from the functional limitation profile.[26] If applicable, we measured effects on the carer using the carer strain index.[27] Lung function was assessed by spirometry. Upper arm movements were assessed because restriction had been noted after ECMO previously.[13] A modified assessment was done in hospital for patients who had not been discharged. If a home visit was unacceptable, patients were offered a telephone interview or postal questionnaire. For those refusing this option, permission was requested for information to be sought from their general practitioner.

Economic evaluation

We designed the study to allow for analysis of both cost-effectiveness and cost-utility from the perspectives of the publicly funded health and social-care sector, and from patients and their families or carers. Methods for the economic study have been extensively described previously.[18] Data about patients' transport and days in hospital at different levels of care were gathered as events occurred during the trial. Data about patients' use of health-care resources after discharge from hospital were gathered with a questionnaire designed for self-completion during a 6-month follow-up visit.

The costs of care received in critical care units, including the ECMO centre, were taken from a large, multicentre study of critical care unit expenditure and case-mix done concurrently with the CESAR trial in England, Scotland, and Northern Ireland.[28] On the basis of this work and previous statistical analyses of the costs of critical care patients,[29] case-mix-adjusted average costs per day within the critical care unit were weighted according to the number of organ systems that were being supported on that day; the number of organ systems being supported were recorded routinely during the trial. The average daily costs of participating critical care units (including the ECMO centre) were estimated with standard definitions according to critical care national cost block methodology with further allowance for capital equipment.[30,31,32] Hospital overheads such as heating, lighting, and management costs were not included. Costs of the remaining time spent in hospital were estimated from previously published daily rates;[33,34] unit costs of care after discharge were based on the same sources.

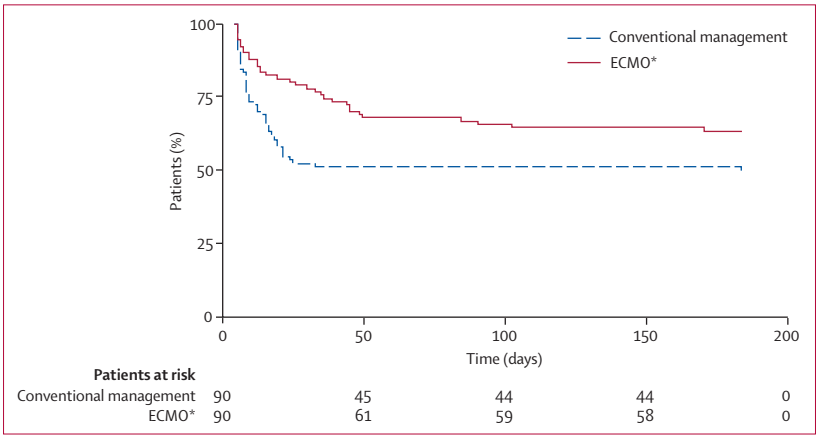

Figure 2: **Kaplan-Meier survival estimates**
ECMO=extracorporeal membrane oxygenation. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment.

	ECMO group (n=90)*	Conventional management group (n=90)
All patients		
Critical care (days)	24·0 (13·0–40·5)†	13·0 (11·0–16·0)
Hospital (days)	35·0 (15·6–74·0)	17·0 (4·8–45·3)
Patients who died‡		
Critical care (days)	11·0 (2·0–28·0)†	5·0 (2·0–13·5)
Hospital (days)	15·0 (3·0–40·5)	5·0 (2·0–13·5)

Data are median (IQR). ECMO=extracorporeal membrane oxygenation. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. †Excludes one patient whose notes are still with the coroner. ‡Data for 33 patients receiving extracorporeal membrane oxygenation, and 45 patients receiving conventional management.

Table 4: **Length of stay**

	ECMO group (n=90)*	Conventional management group (n=90)
Alive at 6 months or discharged alive	57 (63%)	46 (51%)
Follow-up information available†		
Full information	52 (58%)	32 (36%)
Incomplete information from GP or hospital	5 (6%)	8 (9%)
Information about death and disability status only	0	3 (3%)
Alive but no further information available	0	3 (3%)
EQ-5D		
Follow-up information available	57 (63%)	40 (44%)
Problems with mobility		
None	30 (33%)	19 (21%)
Some	26 (29%)	19 (21%)
Confined to bed	0	2 (2%)
Data missing	1 (1%)‡	0
Problems with self care		
None	42 (47%)	26 (29%)
Some problems washing or dressing	13 (14%)	11 (12%)
Unable to wash or dress	2 (2%)	2 (2%)
Data missing	1 (1%)‡	1 (1%)§
Follow-up information available	52 (58%)	33 (37%)
Problems with usual activities		
None	21 (23%)	10 (11%)
Some	25 (28%)	19 (21%)
Unable	6 (7%)	4 (4%)
Pain or discomfort		
None	23 (26%)	13 (14%)
Moderate	22 (24%)	18 (20%)
Extreme	7 (8%)	2 (2%)
Anxiety or depression		
None	23 (26%)	21 (23%)
Moderate	26 (29%)	9 (10%)
Extreme	3 (3%)	3 (3%)
Overall health status (VAS; 0–100)¶	67·9 (2·8)	65·9 (3·8)
Follow-up information available	52 (58%)	33 (37%)
Data missing	0	1 (1%)
Compared with 1 year ago		
Better now	9 (10%)	2 (2%)
Somewhat better now	5 (6%)	2 (2%)
About the same	9 (10%)	5 (6%)
Somewhat worse now	18 (20%)	13 (14%)
Much worse now	11 (12%)	9 (10%)
Data missing	0	1 (1%)
SF-36 (0–100)¶		
Physical functioning	64·5 (4·2)	60·0 (5·9)
Physical role	58·2 (4·8)	46·3 (6·5)
Bodily pain	66·2 (4·2)	62·2 (5·0)
General health	54·1 (3·0)	49·3 (3·9)
Vitality	52·9 (3·3)	47·7 (4·1)
Social functioning	69·5 (3·9)	62·1 (5·7)
Emotional role	72·6 (4·3)	71·4 (5·6)
Mental health	70·5 (3·0)	65·5 (3·7)
Data missing	2 (2%)‡	1 (1%)

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Patients' health-related quality of life was measured with EQ-5D at 6 months after randomisation; we assumed that all patients had a zero quality-of-life score at randomisation. Quality-adjusted life-years (QALYs) were calculated from UK tariff values for EQ-5D health states.[22]

We did cost-effectiveness and cost-utility analyses using effectiveness of treatment and resource-use data obtained from the clinical trial, and used bootstrap methods to estimate the uncertainty around the estimated results generated for the cost-utility analyses.[35] Sensitivity analysis was undertaken for key cost variables; in place of case-mix-adjusted costs, we calculated the costs of care received in the critical care unit care using NHS reimbursement costs per day in an intensive care unit. Complete case analysis was used for the base-case analysis of both cost-effectiveness and cost-utility. We imputed missing data for sensitivity analysis using Rubin's multiple imputation method[36] with SOLAS (version 3.20).

Lifetime incremental cost-utility was estimated with several simplifying assumptions: (1) age-specific and sex-specific life expectancy for each surviving patient in the trial was calculable from UK life tables;[37] (2) at 24 months after randomisation, all surviving patients attained the same average life expectancy and health state as adults of similar age in the UK population;[31,38–41] (3) average health states for different age-groups could be obtained from the 1996 health survey for England;[42] and (4) at 24 months after randomisation, the average health-service expenditure for surviving patients was the same as that of similar age-groups in the UK. Patients were separated into age-groups of 18–44 and 45–64 years. Data for health services costs for these age-groups have been published in the proceedings of Parliament.[43] The same age-groups were used as the basis for estimating patients' long-term costs and benefits. For the lifetime estimates, costs and QALYs were discounted at 3·5%, based on UK treasury guidelines.[44]

All costs were measured as they occurred during the trial period but are reported at 2005 price levels in GB pounds. We also report values in US dollars using Organisation of Economic Co-operation and Development purchasing power parity values.[45]

Statistical analysis

Power calculations were based on an anticipated 70% mortality in the conventional management group. Assuming a 10% risk of severe disability in surviving patients in both treatment groups, at $\alpha=0\cdot05$ (two-sided) and $\beta=0\cdot2$, 120 patients would be required in each group (240 in total) to detect reduction by a quarter in the proportion of patients achieving the primary outcome from 73% to 55%. This estimate was conservative based on descriptive studies of adult ECMO.[10,11] Several other scenarios were shown on a sample size grid in the

published protocol.[13] The target sample size was reviewed in June, 2003, by the independent data monitoring committee when the sample size was 63 (less than 60% of target). The proportion of patients achieving the primary outcome in the conventional management group was 67%, and therefore a lower sample size (180 patients) was expected to detect reduction by a third.

Primary analysis was by intention to treat. We compared treatment groups using the χ^2 test for dichotomous variables, *t* tests for continuous variables, non-parametric tests for median values where appropriate, and the log-rank test for time-to-event data. Secondary analyses included subgroup analyses based on the minimisation criteria at trial entry, and a per-protocol analysis. The data monitoring committee reviewed interim analyses in strict confidence on seven occasions. They were charged with informing the trial steering committee if proof beyond reasonable doubt (based on Haybittle[46] and Peto's[47] stopping guidelines) suggested that any part of the protocol under investigation was either clearly indicated or contra-indicated (for all patients, or a specific subgroup), or that no clear outcome would be obtained with the chosen trial design. Except for individuals who supplied confidential information, all study personnel (including the steering committee, funders, collaborators, and administrative staff) were masked from results of the interim analysis.

This study is registered, number ISRCTN47279827.

Role of the funding source

The sponsors of the study had no input in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for decision to submit for publication.

Results

Between July, 2001, and August, 2006, enquiries were made about 766 potentially eligible patients from 148 centres, of whom 180 were enrolled from 68 centres and randomly allocated (figure 1). Table 1 shows the demographic characteristics of these patients at baseline.

68 (75%) patients considered for treatment with ECMO actually had ECMO support, and most of the remaining patients (n=17) had conventional management (table 2); median duration of treatment was slightly shorter for patients allocated to consideration for treatment by ECMO than for those receiving conventional management. Low-volume low-pressure ventilation was achieved in more patients and on a greater proportion of days for patients allocated to consideration for treatment by ECMO than for those receiving conventional management. Steroids were used in more patients in the consideration for ECMO group than the conventional management group, and molecular albumin recirculating system for liver dysfunction was used in almost a fifth of patients in the consideration for ECMO group compared with none receiving conventional management.

Of the 90 patients randomly allocated for consideration to receive ECMO, three died before transport, two died in transit, and 85 arrived successfully at the ECMO centre. 17 patients were treated with gentle ventilation of whom 14 survived, and 68 were treated with ECMO

	ECMO group (n=90)*	Conventional management group (n=90)
(Continued from previous page)		
St George's respiratory questionnaire (0–100)‖		
Symptom score	32·4 (3·3)	41·2 (4·5)
Data missing	0	1 (1%)
Activity score	29·5 (3·7)	38·4 (5·4)
Data missing	2 (2%)‡	0
Impacts score	15·0 (2·4)	18·8 (3·1)
Total score	22·4 (2·7)	27·6 (3·6)
Data missing	2 (2%)‡	1 (1%)
Mini mental state examination score (0–30)¶	28·6 (0·3)	28·0 (0·5)
Below normal (<24)	2 (2%)	2 (2%)
Data missing	3 (3%)§	1 (1%)
HADS depression score (0–21)‖	4·4 (0·6)	5·8 (0·7)
Clinically significant depression (score 11–21)	4 (4%)	4 (4%)
Data missing	2 (2%)	0
HADS anxiety score (0–21)‖	5·8 (0·6)	7·4 (0·8)
Clinically significant anxiety (score 11–21)	7 (8%)	10 (11%)
Data missing	2 (2%)	0
Sleep problems score (0–100)‖	16·7 (3·2)	18·8 (3·6)
Carergiver strain index (0–12)‖		
Low	8 (9%)	2 (2%)
High (≥7)	9 (10%)	6 (7%)
Data missing	2 (2%)§	0
Not applicable (no carer)	33 (37%)	24 (27%)
Restrictions to upper limb movements	3 (3%)	5 (6%)
Data missing	2 (2%)§	1 (1%)
Lung capacity		
FEV_1 (L; percent of predicted value)	2·6 (0·1); 74·9% (2·0)	2·5 (0·1); 72·9% (3·3)
FVC (L; percent of predicted value)	3·3 (0·1); 79·6% (2·4)	3·2 (0·2); 79·9% (3·6)
FER (L; percent of predicted value)	81·9 (1·5); 101·0% (1·7)	81·6 (2·2); 100·7% (2·5)
PEFR (L; percent of predicted value)	370·7 (16·1); 74·5% (2·4)	364·3 (20·5); 75·1% (3·6)
Data missing	3 (3%)	2 (2%)

Data are number (%) or mean (SE). ECMO=extracorporeal membrane oxygenation. GP=general practitioner. EQ-5D=EuroQol-5 dimensions. VAS=visual analogue scale. HADS=hospital anxiety and depression scale. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. FER=forced expiratory ratio (FEV_1/FVC). PEFR=peak expiratory flow rate. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. †Follow-up information was available for the numbers of patients shown for all assessments unless otherwise indicated. ‡One patient in a wheelchair and did not answer mobility question, and one patient had limited mobility so left out those sections. §Severe alcohol related problems so very limited follow up available. ¶Higher score indicates better condition. ‖Higher score indicates worse condition.

Table 5: **Follow-up assessment at 6 months**

	ECMO group (n=90)*		Conventional management group (n=87)		Incremental cost-effectiveness ratio†
	Mean cost	Probability of survival to 6 months	Mean cost	Probability of survival to 6 months	
Scenario 1: base case‡	£73 979	0·63	£33 435	0·47	£250 162; US$404 268
Scenario 2: QALYs gained at 6 months with costs based on NHS tariffs§	£57 534	0·63	£36 688	0·47	£128 621; US$207 854

ECMO=extracorporeal membrane oxygenation. QALYs=quality-adjusted life-years. NHS=national health service. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. †Ratio of difference in costs to difference in effects. ‡Total days spent in critical care were grouped into three categories based on number of organs supported (0–1, 2, or ≥3), and valued accordingly. Average unit costs applied for all other resource use. §Total days spent in critical care were grouped into three categories (days in extracorporeal membrane oxygenation unit, intensive care unit, or high dependency unit), and average costs applied. Average unit costs applied for all other resource use. Complete-case analysis used.

Table 6: **Cost-effectiveness of allocation to extracorporeal membrane oxygenation versus conventional management**

of whom 43 survived. For patients with information about severe disability, 57 (63%) allocated to consideration for treatment by ECMO had survived without severe disability at 6 months after randomisation compared with 41 (47%) receiving conventional management (table 3). Only one patient, who was receiving conventional management, was known to be severely disabled. A greater proportion of patients in the consideration for ECMO group survived to 6 months than did those in the conventional management group (table 3). Time from randomisation to death was substantially shorter for patients receiving conventional management than for those allocated to consideration for treatment by ECMO (log-rank test p=0·027; figure 2). Most deaths (60%) in the conventional management group were due to respiratory failure, whereas this disorder caused 24% of deaths in patients allocated to consideration for treatment by ECMO; most deaths (42%) in the consideration for ECMO group were due to multiorgan failure, and this disorder caused 33% of deaths in patients receiving conventional management (table 3). Patients allocated to consideration for treament by ECMO spent longer in critical care, and in hospital, than those allocated to conventional management, especially those who ultimately died (table 4).

See Online for webappendix

Two serious adverse events were reported to the data monitoring committee during the study, both in patients allocated to consideration for treatment by ECMO. The first was caused by a mechanical failure of the oxygen supply in the ambulance resulting in the death of the patient during transfer to the ECMO centre. The second was vessel perforation during cannulation; the perforation was controlled, but the clinical team felt that it contributed to the patient's demise. A second death occurred in a patient allocated to consideration for treatment by ECMO during transport, which was due to catastrophic pulmonary haemorrhage and was believed to be caused by the underlying disease, and therefore was not reported as a serious adverse event. No other serious complications of conventional management, ECMO, or transport occurred.

Table 5 shows data from the 6-month follow-up assessment. The first two EQ-5D questions about mobility and self care were used to define severe disability in our primary outcome, and were answered by proxy for five patients in the ECMO group and seven in the conventional management group. Consequently, the number of patients with missing data are lower than for other components of EQ-5D, and other follow-up and economic assessments. No significant differences were recorded between groups for any follow-up assessments. Although final primary outcome data for clinical efficacy were available from all but three patients, complete EQ-5D data were missing in 17 cases.

Mean health-care costs per patient were more than twice as high for patients allocated to consideration for treatment by ECMO than for those allocated to conventional management, with a difference in costs of £40 544 (95% CI 24 799–56 288 [US$65 519, 40 076–90 963]; table 6). As is usual, health-care costs were skewed and highly variable between patients. Details of resource use and cost are shown in webappendix pp 1–2. Table 6 shows the incremental cost-effectiveness of referral for ECMO per additional surviving patient without severe disability for the base-case analysis and the sensitivity analysis for alternative methods for cost estimation.

Table 7 reports the incremental cost-utility ratios for different scenarios from the NHS perspective, with results given for the cost-utility analysis according to changes in key assumptions. Allocation to ECMO was associated with a mean gain in QALYs at 6 months after randomisation compared with conventional management; table 7 shows the cost per additional QALY. Individual patient costs estimated with the number of days at different levels of critical care and the national NHS prices as the source of unit cost (rather than the number of days at different levels of organ support and unit costs obtained from participating centres) are shown in scenario 2 in tables 6 and 7, and in both cases reduce costs per outcome gained from the consideration for ECMO treatment option. We have also calculated the predicted lifetime incremental cost per QALY with discount rates at 3·5% (scenario 3), and 0% (scenario 4, future values would be worth the same as current values); at 0%, total costs and total QALY gain were both higher, and the cost-utility of ECMO improves (table 7).

The confidence intervals in these estimates indicate that the cost-utility analysis is associated with substantial uncertainty (table 7). Estimation with the cost-effectiveness acceptability method[18] of the probability that a policy of consideration for ECMO would be cost-effective at different thresholds of willingness to pay in GP pounds (2005), shows that consideration for ECMO has more than 50% probability of being cost effective at

	QALYs gained (95% CI)	Additional cost	Incremental cost-effectiveness ratio (95% CI)*
Scenario 1: QALYs gained at 6 months with costs based on primary research study†	0·03 (0·00–0·06)	£44 191	£1 631 124 (–3 242 953 to 11 463 378); US$2 635 933 (–5 240 683 to 18 525 072)
Scenario 2: QALYs gained at 6 months with costs based on NHS tariffs‡	0·03 (0·00–0·06)	£26 772	£732 818 (223 832 to 491 808); US$1 184 250 (361 718 to 7 948 741)
Scenario 3: lifetime-predicted costs and QALYs, discounted at 3·5%‡	3·66 (··)	£48 533	£19 252 (7 622 to 59 200); US$31 112 (12 317 to 95 507)
Scenario 4: lifetime-predicted costs and QALYs, no discount‡	7·01 (··)	£53 896	£9 389 (4 580 to 31 877); US$15 183 (7 401 to 51 514)

QALYs=quality-adjusted life-years. NHS=national health service. ··=data not calculated. *Ratio of difference in costs to difference in effects. †Complete-case analysis used. ‡Multiple imputation of missing data used.

Table 7: **Cost-utility analysis results for CESAR trial (bootstrap estimates)**

any expenditure threshold of more than about £20 000 ($33 000) per QALY.

Discussion

This study shows a significant improvement in survival without severe disability at 6 months in patients transferred to a specialist centre for consideration for ECMO treatment compared with continued conventional ventilation. For patients allocated to receive conventional management, outcome at 6-month follow-up was better than predicted when planning the study. However, outcome was even better for patients allocated for consideration to receive ECMO than for those allocated to receive conventional management. Mortality alone was also lower in the consideration for ECMO group than in the conventional management group, but the study was not powered to detect this outcome and the difference did not reach statistical significance. The quality of life and spirometry results at 6 months were better than that reported in previous studies for both treatment groups.[48,49] Although this effect could have been caused by participation in a trial, the definitive cause is unknown.

Several factors could account for the improved outcome for patients allocated to consideration for treatment by ECMO. First, ECMO sustains life in acute lung failure long enough for diagnosis, treatment, and recovery. ECMO rests the lungs from high pressure and FiO_2 ventilation, thereby keeping to a minimum the iatrogenic contribution to lung injury. Correspondingly, we recorded a significant increase in the proportion of lung-protective ventilation in the consideration for ECMO group compared with the conventional management group. We believe that this effect indicates the advanced nature of lung injury in patients recruited into the CESAR trial, which means that these patients could not be ventilated gently without extracorporeal gas exchange. Risks associated with ECMO were small, but the procedure is complex and labour intensive, even in a highly experienced centre such as Glenfield Hospital, and at present very sick patients must undergo transfer to the centre. Three patients died before they could be transferred and two died in transit. If cannulation at the referring hospital and mobile ECMO support could be used for such patients, survival rates might be further improved.[50,51]

Second, the study used a standardised protocol for disease management in a highly experienced centre. A fifth of patients treated at Glenfield Hospital improved on that protocol without the need for ECMO, of whom 82% survived to discharge. We believe that the lung disease in these patients was slightly less severe than in the four-fifths of patients who did not respond to conventional management and received ECMO, of whom 63% survived. We used careful minimisation to ensure that control and treatment groups were identical, therefore we expect that if the same protocol was uniformly applied in patients allocated to conventional management in conventional treatment centres, similar proportions of patients would have had similar proportions of patient survival. The possibility of bias caused by treatment preference of the clinical teams was eliminated by the design of the study because the ECMO team did not treat patients in the conventional management group, except for transferring 11 patients from referral hospitals to conventional treatment centres, none of whom died during transfer. A team treating a high volume of patients with a particular illness is expected to achieve good results compared with units that might treat such severe respiratory failure only once or twice per year. However, we emphasise that only a fifth of patients treated responded to expert conventional respiratory intensive care, and the remainder needed ECMO to achieve lung rest. Since very few patients with acute respiratory distress syndrome are transferred to other units for expert conventional care in the UK, the pragmatic design of our study examines the realistic situation for such patients.

With the exception of use of the molecular albumin recirculating system and steroids, use of ancillary treatments was the same in both groups, and no conclusions can be drawn regarding the effectiveness of these treatments. Steroids are used in late fibrotic acute respiratory distress syndrome; more patients in the ECMO group survived long enough to enter this late stage of disease, which could account for the increased steroid use. The molecular albumin recirculating system was used for liver dysfunction from multiorgan failure in 15 patients allocated to ECMO, and might have also contributed to their lengthened survival.

Our study was limited by the absence of a standardised treatment protocol in the conventional management group, which was largely caused by the inability of participating units to reach a consensus on the constituents of best treatment. These units were not willing to participate in the study if a protocol was imposed. We considered transferring patients from both treatment groups to the ECMO unit, but participating units did not judge the ECMO unit to be competent providers of conventional management or intensive care, and were concerned about the ECMO unit's possible bias in favour of ECMO. We also rejected the possibility of transferring all control patients to one expert centre for conventional treatment since no centre had the necessary capacity. No NHS funding was available for this referral practice in the context of the trial, and participating units were unwilling to send patients to another unit when they did not perceive a treatment advantage. To secure the collaboration of participating units, we had to allow them freedom to choose a protocol for conventional management. The low-volume low-pressure ventilation strategy of the ARDSNet study[19] was recommended, but no specific treatment protocol was imposed.

A randomised trial of a life-support technique in acute fatal illness is associated with unique ethical and logistical problems, especially when the endpoint includes death. ECMO, for example, is potentially expensive, and physicians and patients cannot be masked at treatment delivery. Families are told that the patient has a high probability of death from acute lung failure, and then asked to consent to a life-saving technique that is only available, but not guaranteed, if they agree to enrolment in the study. In a study in one centre, a patient on the life-support technique could possibly be next to a patient on conventional treatment. Crossover can dilute these effects but such a design can make the results of the study difficult to interpret because of the composite endpoint. For example, treatment failure in one group of a crossover study leads to change to the other treatment, and the endpoint then becomes death or ECMO, which in uninterpretable. Because of these problems, ECMO has been investigated with other designs such as matched-pair studies, adaptive design randomised controlled trials, and conventional randomised controlled trials.[7,8,16,52–54] The influential UK neonatal ECMO trial[16] compared the best available standard treatment in several experienced centres with the ECMO treatment algorithm in five specialist centres. We built on this study design in the CESAR trial, in which the families of only 33 eligible patients refused consent and treating intensivists refused to enter 28 patients. Our experience is that our design comes closest to a solution for randomised trials in patients with acute illness and high risk of death, while keeping ethical and logistical barriers to a minimum.

We have shown that the additional average cost per patient of referral for ECMO is more than double the average cost of treatment with conventional management. The lifetime predicted cost-utility of about £19 000 ($31 000) per QALY is, however, well within the range regarded as cost effective by health technology assessment organisations. Furthermore, the number of patients with severe respiratory failure is small compared with other diseases, and so the effect on the health-care budget would also be small. The uncertainty around cost-effectiveness estimates underscores the wide range of predicted effects of ECMO treatment; such uncertainty is frequently the case in health-care planning, and an insurance-risk model of financing is needed. However, we have shown that referral for ECMO is likely to prove more efficient than conventional management.

Our findings are relevant to other countries where ECMO is provided or being considered, although local costs, health services, practice, and distances from treatment centres might vary. The uncertainty around cost-effectiveness estimates indicates the combination of uncertainty in the trial data about patients' severity of illness, treatment outcomes, health systems, and costs. Further uncertainty is introduced in prediction of costs for the future and other settings. We found that our hospital cost estimates were sensitive to methods used to estimate costs in critical care units. National data about costs of NHS critical care were not available at the outset of our study, but are now published as tariffs for providers (NHS hospital trusts)[8] to use in contracts with third party payers. Although these costs are likely to be reliable estimates of true resource costs, the NHS financial system uses different values (not case-mix-adjusted) that predict reduced costs per outcome gained.

The cost-effectiveness of ECMO would be improved if costs of both transport and provision of the technique could be reduced. These two factors might be inversely related. Provision of ECMO will probably be most clinically and economically efficient (reduced cost per successful case treated) in large critical care units, and the clinical effectiveness of small units would be lower than that of busy units. However, long-distance air travel could be kept to a minimum with a large number of well placed critical care units, which would inevitably be small and less economically efficient than large units. In our trial, almost all air transport was provided by the Royal Air Force (RAF), which was quite expensive, and unrealistic since the RAF is not a routine service provider for the NHS. Air transport costs could be reduced by use of a dedicated air ambulance for patient retrieval. We recommend further careful modelling of the most cost-effective solution for different settings.

We are confident that ECMO is a clinically effective treatment for acute respiratory distress syndrome,

which also promises to be cost effective in comparison with other techniques competing for health resources.

Contributors

GJP was lead clinical investigator. MM was lead investigator for economics input, and MMT and CLH were investigators for economics input. AW was lead investigator for patient follow-up. DE was lead investigator for statistics, and study design and management. All authors were members of the project management team. AT and GJP obtained ethical approval for the study. RT, AT, GJP, and RKF participated in recruitment of centres or patients, or both. GJP, AW, EA, AT, FC, NC, RKF, and DE participated in study design and data collection; MM, MMT, CLH participated in the study design and data collection for economics research; and RT participated in data collection for clinical research. DE, EA, MM, and CLH participated in data analysis. All authors participated in data interpretation and reporting of results. All authors have seen and approved the final version.

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For all other hospitals supplying data, we have listed each hospital with the names of collaborating medical staff.
Addenbrookes Hospital, Cambridge; *Amersham Hospital, Amersham*; *Biggleswade Hospital, Biggleswade*; *Cannock Chase Hospital, Cannock*; *Chapel Allerton Hospital, Leeds*; *Coventry & Warwickshire Hospital, Coventry*; *Freeman Hospital, Newcastle upon Tyne*; *Goodmayes Hospital, Illford*; *Hammersmith Hospital, London*; *Harefield Hospital, Harefield*; *Hawthornes Care Centre, Peterlee*; *Hope Hospital, Salford*; *Leigh Infirmary, Wigan*; *Lister Hospital, Stevenage*; *Mile End Hospital, London*; *North Middlesex Hospital, London* (A Chan, R Lo, GL Dabuco, N Mathew); *Northwick Park Hospital, London*; *Papworth Hospital, Cambridge*; *St James's University Hospital, Leeds*; *St Thomas' Hospital, London*; *Southern General Hospital, Glasgow* (M Garrioch); *University Hospital, North Tees, Hartlepool* (P Ritchie, F Bage, L Williams, J Tint); *Wythenshawe Hospital, Manchester*.

Conflicts of interest

GJP, RKF, and RT are clinicians who provide extracorporeal membrane oxygenation services. GJP received a travel grant to present results of the CESAR trial at the Children's National Medical Centre conference (February, 2008) from Chalice Medical. RKF received a travel grant to attend the Extracorporeal Life Support Organization meeting (September, 2008) from Chalice Medical. All other authors declare that they have no conflicts of interest.

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References

1 Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004; **30**: 51–61.

2 Bersten AD, Edibam C, Hunt T, Moran J; Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian states. *Am J Respir Crit Care Med* 2002; **15:** 443–48.

3 Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. *Chest* 2007; **131:** 554–62.

4 Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomised, controlled trial. *Am J Respir Crit Care Med* 2002; **166:** 801–08.

5 Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005; **171:** 340–47.

6 Mancebo J, Fernandez R, Blanch, L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; **173:** 1233–39.

7 Morris AH, Wallace CJ, Menlove RL, et al. Randomised clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; **149:** 295–305.

8 Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomised prospective study. *JAMA* 1979; **242:** 2193–96.

9 Vasilyev S, Schaap RN, Mortensen JD. Hospital survival rates of patients with acute respiratory failure in modern respiratory intensive care units. An international, multicenter, prospective survey. *Chest* 1995; **107:** 1083–88.

10 Kolla S, Awad SS, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH. Extracorporeal life support for 100 adult patients with severe respiratory failure. *Ann Surg* 1997; **226:** 544–64.

11 Peek GJ, Moore HM, Moore N, Sosnowski AW, Firmin RK. Extracorporeal membrane oxygenation for adult respiratory failure. *Chest* 1997; **112:** 759–64.

12 Van Meurs K, Lally KP, Peek GJ, Zwischenberger JB, eds. ECMO extracorporeal cardiopulmonary support in critical care, 3rd edn. Ann Arbor, MI: Extracorporeal Life Support Organisation, 2005.

13 Peek GJ, Clemens F, Elbourne D, et al. CESAR: conventional ventilatory support vs extracorporeal membrane oxygenation for severe adults respiratory failure. *BMC Health Serv Res* 2006, **6:** 163.

14 Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **138:** 720–23.

15 Peek GJ, Tirouvopaiti R, Firmin RK. Extracorporeal life support in cardio-pulmonary critical care, 3rd edn. Ann Arbor, MI: Extracorporeal Life Support Organisation, 2005.

16 UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996; **348:** 75–82.

17 UK Collaborative ECMO Group. The collaborative UK ECMO (extracorporeal membrane oxygenation) trial: follow-up to 1 year of age. *Pediatrics* 1998; **101:** E1.

18 Thalanany MM, Mugford M, Hibbert C, et al. Methods of data collection and analysis for the economic evaluation alongside a national, multi-centre trial in the UK: conventional ventilation or ECMO for severe adult respiratory failure (CESAR). *BMC Health Serv Res* 2008; **8:** 94.

19 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342:** 1301–08.

20 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13:** 818–29.

21 Ware JE. SF-36 health survey-manual and interpretation guide. Boston, MA: Nimrod Press, 1993.

22 The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208.

23 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St George's respiratory questionnaire. *Am Rev Respir Dis* 1992; **145:** 1321–27.

24 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 2006; **67:** 361–70.

25 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* 1975; **12:** 189–98.

26 Williams, SJ. Measuring health status? A review of the sickness impact and functional limitations profile. *Health Care Anal* 2006; **4:** 273–83.

27 Robinson BC. Validation of a caregiver strain index. *J Gerontol* 1983; **38:** 344–48.

28 Hibbert C. Development and application of a method for estimating case-mix adjusted costs of adult critical care units. Sheffield: University Sheffield; 2007.

29 Stevens VG, Hibbert CL, Edbrooke DL. Evaluation of proposed case-mix criteria as a basis for costing patients in the adult general intensive care unit. *Anaesthesia* 1998; **53:** 944–50.

30 Dean JE, Edbrooke DL, Corcoran MC. The critical care national cost block programme: implementing a standard costing methodology on a national scale. *Care Crit Ill* 2002; **18:** 3.

31 Graf J, Wagner J, Graf C, Koch KC, Janssens U. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients—a cost-utility analysis. *Crit Care Med* 2005; **33:** 547–55.

32 Edbrooke D, Hibbert C, Ridley S, Long T, Dickie H. The development of a method for comparative costing of individual intensive care units. The Intensive Care Working Group on Costing. *Anaesthesia* 1999; **54:** 110–20.

33 Curtis L, Netten A. Unit costs of health and social care 2005. London: University of Kent, 2005.

34 Department of Health. NHS reference costs 2005. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4133221 (accessed Aug 12, 2009).

35 Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997; **6:** 327–40.

36 Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: John Wiley & Sons, 1987.

37 Government Actuary's Department. Life tables for the UK. 2007. http://www.gad.gov.uk/Demography%20Data/Life%20Tables/Interim_life_tables.html (accessed Aug 12, 2009).

38 Angus DC, Musthafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001; **163:** 1389–94.

39 Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; **348:** 683–93.

40 Rimachi R, Vincent JL, Brimioulle S. Survival and quality of life after prolonged intensive care unit stay. *Anaesth Intensive Care* 2007; **35:** 62–67.

41 Sznajder M, Aegerter P, Launois R, Merliere Y, Guidet B, CubRea. A cost-effectiveness analysis of stays in intensive care units. *Intensive Care Med* 2001; **27:** 146–53.

42 Department of Health. Health survey for England 1996. http://www.dh.gov.uk/en/Publicationsandstatistics/PublishedSurvey/HealthSurveyForEngland/Healthsurveyresults/DH_4001554 (accessed Aug 12, 2009).

43 HM Government. Commons Hansard: parliamentary proceedings (Dec 14, 2004). http://www.publications.parliament.uk/cgi-bin/newhtml_hl?DB=semukparl&STEMMER=en&WORDS=health%20expenditur&ALL=health%20expenditure&ANY=&PHRASE=&CATEGORIES=&SIMPLE=&SPEAKER=&COLOUR=red&STYLE=s&ANCHOR=41214w25.html_spnew6&URL=/pa/cm200405/cmhansrd/vo041214/text/41214w25.htm#41214w25.html_spnew6 (accessed Aug 12, 2009).

44 HM Treasury. The green book: appraisal and evaluation in central government. London: Stationery Office, 2007.

45 Organisation for Economic Cooperation and Development. OECD statistics on purchasing power parities (PPP). http://www.oecd.org/statisticsdata/0,3381,en_2649_34357_1_119656_1_1_1,00.html (accessed Aug 12, 2009).

46 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971; **44:** 793–97.

47 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; **34:** 585–612.

48 Davidson TA, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA* 1999; **281:** 354–60.

49 Orme J Jr, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2003; **167:** 690–94.

50 Foley DS, Pranikoff T, Younger JG, et al. A review of 100 patients transported on extracorporeal life support. *ASAIO J* 2002; **48:** 612–19.

51 Hemmila MR, Rowe SA, Boules TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg* 2004; **240:** 595–605.

52 Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: a prospective randomised study. *Pediatrics* 1985; **76:** 479–87.

53 O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomised study. *Pediatrics* 1989; **84:** 957–63.

54 Bifano EM, Hakanson DO, Hingre RV, Gross SJ. Prospective randomised controlled trial of conventional treatment or transport for ECMO in infants with persistent pulmonary hypertension (PPHN). *Pediatr Res* 1992; **31:** 196A.

Ventilatory support versus ECMO for severe adult respiratory failure

Giles Peek and colleagues (Oct 17, p 1351)[1] report an improved outcome in patients with severe acute respiratory failure who were treated in one centre according to a management protocol based on extracorporeal membrane oxygenation (ECMO) when compared with conventional therapy in less specialised hospitals.

Remarkably, 25% of the transferred patients were already managed successfully with conventional treatment options covering low tidal volume ventilation with pressure limitation, titrated positive end-expiratory pressure, restrictive fluid management, prone positioning, and steroid medication. Inhaled nitric oxide (iNO) was used only in about 10% of the patients, although iNO is regarded as feasible rescue treatment in acute lung injury if refractory hypoxaemia develops.[2]

In the controlled phase 2 study by Dellinger and colleagues,[3] application of iNO to patients with acute lung injury induced a significant improvement in the oxygenation index (defined as product of PaO_2 and FiO_2 divided by the value of mean airway pressure) over several days, thus showing a reduction in the invasiveness of mechanical ventilation. Two other studies that assessed the effects of iNO in patients with acute lung injury or acute respiratory distress syndrome have shown either a reduced ECMO frequency[4] or a reduction in the incidence of severe respiratory failure (corresponding to ECMO entry criteria).[5]

It remains to be seen whether a systematic incorporation of iNO into the therapy algorithm as a primary approach for the treatment of refractory hypoxaemia might further contribute to reducing the need for ECMO without compromising event-free survival in patients with severe acute respiratory failure.

We declare that we have no conflicts of interest.

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1 Peek GJ, Mugford M, Tiruvoipati R, et al, for the CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374:** 1351–63.

2 Germann P, Braschi A, Della Rocca G, et al. Inhaled nitric oxide therapy in adults: European expert recommendations. *Intensive Care Med* 2005; **31:** 1029–41.

3 Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. *Crit Care Med* 1998; **26:** 15–23.

4 Gerlach H, Keh D, Semmerow A, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. *Am J Respir Crit Care Med* 2003; **167:** 1008–15.

5 Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. *Intensive Care Med* 1999; **25:** 911–19.

Giles Peek and colleagues[1] describe the beneficial effects of extracorporeal membrane oxygenation (ECMO) in patients with severe acute respiratory distress syndrome.

Peek and colleagues state that the primary outcome measure was death or severe disability at 6 months after randomisation. Later, however, they note that the study was not powered to detect mortality as an outcome. Moreover, the study was powered on an expected 70% mortality in the conventional group, and in 2003 the sample size was reduced from 240 to 180, although Peek and colleagues might have done an additional review of the sample size before ending the study.

In the ECMO group, treatment with low-volume, low-pressure ventilation was significantly more frequent than in the conventional group in the other hospitals. This finding suggests a difference in protocol between the single ECMO centre, Glenfield Hospital, and the rest of the 92 intensive-care units. The ECMO group (n=90) contained 22 patients who underwent conventional treatment. These patients were analysed with an intention-to-treat approach, but they seem to represent an entirely different third group.

Finally, Peek and colleagues show that the molecular albumin recirculating system (MARS) was only used in the ECMO group for liver dysfunction, which may have had a role in survival. It is not clear whether MARS was only available at Glenfield Hospital or whether patients with ECMO had an increased risk of liver dysfunction.

The most important conclusion that can be drawn from this study is that there is a significant improvement in survival without severe disability at 6 months in patients transferred to Glenfield Hospital compared with 92 other intensive-care units. Whether it was due to ECMO, hospital-related factors, or a strict ventilation protocol in the conventional group is still not clear.

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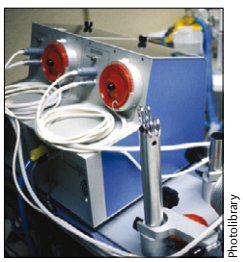
We congratulate Giles Peek and co-workers[1] for successfully doing a study of the effect on survival of extracorporeal membrane oxygenation (ECMO) in patients with severe lung failure. Nevertheless, we have some criticisms that might be relevant to the interpretation of the data.

First, patients in the control group were not treated according to a specific management protocol, but with the "best critical care practice available in their centre". As a result,



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only 70% of the control group were ventilated by low-tidal-volume and low-pressure ventilation according to the recommendations of the Acute Respiratory Distress Syndrome (ARDS) Network.[2] The absence of a strict lung protection protocol for the control group will undoubtedly have affected survival, since such a strategy can reduce mortality from 39·8% to 31·0%.[2] Use of a lung protective ventilation strategy in the CESAR control group might well have cancelled out the significant difference between both groups. Moreover, it remains ambiguous to what extent survival rates are affected by the circumstance that 22 patients (24%) in the ECMO group who received low-tidal-volume and low-pressure ventilation according to ARDS-Network recommendations did not receive ECMO treatment.

Second, in the ECMO group, only two serious adverse events were described anecdotally. Such a report is surprising, since all recent ECMO investigations reported an incidence of severe adverse events ranging from 24% to 55%.[3] ECMO is an invasive method with potentially life-threatening complications (bleeding, haemolysis, air leakage, thrombosis), and a complication rate of 3·5 % in the ECMO-treated patients in CESAR calls for explanation beyond advances in cannulation technique, materials, and monitoring.

Third, in recent years, new promising techniques for extracorporeal lung support have been developed,[4,5] yet CESAR used "traditional" ECMO with roller pumps and high anticoagulation. Whether these advances will exert a further increase in survival will have to be elucidated by future studies.

We declare that we have no conflicts of interest.

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2 Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342:** 1301–08.
3 Hemmilla M, Rowe S, Boules TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg* 2004; **240:** 595–607.
4 Bein Th, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 2006; **34:** 1372–77.
5 Cattaneo G, Strauss A, Reul H. Compact intra- and extracorporeal oxygenator developments. *Perfusion* 2004; **19:** 251–55.

We congratulate the authors of the CESAR study[1] on their considerable achievement. However, surely the clearest conclusion from their study is that transfer of the sickest patients to a tertiary centre, which is able to offer both optimum conventional ventilation and advanced techniques (in this case extracorporeal membrane oxygenation [ECMO]), was associated with improved outcomes.

The importance of applying optimum, evidenced-based practice is underlined by the fact that 17 patients (82% of whom survived) in the ECMO group improved with such an approach, and no longer met ECMO criteria. If this level of improvement was replicated even on a smaller scale in the control group, the benefits attributed to the ECMO group would disappear, at least in a study of this size (table).

The CESAR study result is therefore the consequence of two confounding influences: the role of ECMO and the value of regionalisation. However, it still does not establish how ECMO should be used in severe respiratory failure, particularly its use relative to other advanced therapies—eg, high-frequency oscillatory ventilation.

Existing data[2] suggest better outcomes in severe respiratory failure in centres with higher patient volumes. Recent experience with H1N1-related severe respiratory failure in Australasia and Canada,[3,4] and CESAR itself, further support this concept, while also suggesting that there is indeed a role for ECMO. Defining this role beyond rescue therapy, and addressing the wider issue of delivering best practice to more patients than at present, whether through regionalisation, improved local delivery, or most likely both, remain significant challenges for the future.[5]

We declare that we have no conflicts of interest.

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1 Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374:** 1351–63.
2 Kahn JM, Goss CH, Heagerty PJ, et al. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med* 2006; **355:** 41–50.
3 Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; **302:** 1888–95.

	0	–1	–2	–3	–4	–5
Relative risk	0·69	0·71	0·72	0·74	0·76	0·78
95% CI	0·50–0·97	0·51–0·99	0·52–1·02	0·53–1·04	0·54–1·07	0·55–1·10
p value	0·03	0·05	0·07	0·10	0·13	0·17

Analysis based on the 177 patients with complete data on which the primary CESAR outcome reported with Fisher's exact test.

Table: **Sensitivity analysis showing hypothetical effects of decreased occurrence of death or disability (expressed in column headings as number of fewer patients) in control group, assuming no changes in ECMO group**

4 Kumar A, Zarychanski R, Pinto R, for the Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009; **302:** 1872–79.

5 Kahn JM, Asch RJ, Iwashyna TJ, et al. Physician attitudes toward regionalization of adult critical care: a national survey. *Crit Care Med* 2009; **37:** 2149–54.

Authors' reply

In answer to Thilo Busch and colleagues, inhaled nitric oxide (iNO) was used to transport patients who were critically hypoxic or who developed recurrent hypoxia after weaning from extracorporeal membrane oxygenation (ECMO). We are not aware of any studies to show that iNO improves survival in adults. It remains to be seen whether an iNO-based algorithm would reduce the need for ECMO without compromising survival.

We agree with Jayant Jainandunsing and Farouq Ismael that the molecular albumin recirculating system (MARS) was important in the ECMO group. MARS was not prohibited in the conventional group, but no centre elected to use it. It is possible that, by preventing death from respiratory failure, ECMO allowed patients to develop progressive multisystem and liver failure, which required MARS.

We would like to clarify that sample-size adjustments were supported by the independent data monitoring committee on the basis of the primary endpoint of death or severe disability at 6 months. With the exception of data coordinating staff, who reported to the data monitoring committee, the trial team was unaware of the results of the study until after completion.

In answer to Thomas Bein and colleagues, the incidence of serious adverse events in CESAR was about what we expect in our own normal institutional experience.

Although CESAR patients received ECMO using roller pumps, they did not receive high anticoagulation. The evolution of newer extracorporeal systems such as interventional lung assist[1] is interesting, but it is important to recognise their benefits and limitations—ie, interventional lung assist is a carbon dioxide removal device with a reported 10% incidence of leg ischaemia. We encourage workers to report their results to the Extracorporeal Life Support Organization.

Finally, CESAR patients were significantly more hypoxic than those in the ARDS-Network study.[2] This disorder precluded lung-protective ventilation for many patients in the conventional group. We refute the assertion that the conventionally treated patients in the ECMO group constitute a third group. Because of the strict minimisation and equality between the intervention and control groups, the control group must have contained a similar number of patients with equally "mild" respiratory failure.

We agree with the conclusion that survival without severe disability at 6 months was better in the "transfer for consideration of ECMO" group than in the control group. We believe that high-frequency ventilation is useful in the treatment of severe respiratory failure and is complementary to ECMO in achieving lung-protective ventilation.

GJP is a clinician who provides ECMO services. He also received a travel grant to present results of the CESAR trial at the Children's National Medical Centre conference (February, 2008) from Chalice Medical. DE and MM declare that they have no conflicts of interest.

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2 Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342:** 1301–08.

Liraglutide for weight loss in obese people

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For the **Extracorporeal Life Support Organization website** see http://www.elso.med.umich.edu/

Arne Astrup and colleagues (Nov 7, p 1606)[1] report the results of a phase 2 trial in which liraglutide—an analogue of glucagon-like peptide 1 (GLP-1)—was shown to reduce bodyweight in obese patients in a dose-dependent manner. The proposed mode of action is through suppression of appetite and energy intake, and delayed gastric emptying. However, it is important to clarify the possible effect of adverse drug reactions on weight loss.

The incidence of nausea and vomiting increased with dose from 24·2% and 4·2% in those who received 1·2 mg liraglutide daily, up to 47·3% and 11·8% in those who received 3·0 mg. These figures greatly exceeded those for orlistat and placebo, where nausea occurred in 4–5% and vomiting in 2%.

To exclude the possibility that the greater weight loss associated with liraglutide treatment is not mainly a consequence of nausea and vomiting, a comparison of the change in bodyweight between patients who did and patients who did not experience these adverse drug reactions should be presented.

PH received a scholarship in clinical pharmacology from MSD Sweden in 2005. SS and HM declare that they have no conflicts of interest.

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1 Astrup A, Rössner S, Van Gaal L, et al, on behalf of the NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; **374:** 1606–16.

Arne Astrup and colleagues[1] report that treatment of obese individuals with liraglutide, an acylated analogue of glucagon-like peptide 1 (GLP-1), results in more weight loss than placebo or the lipase-inhibitor orlistat.

Liraglutide is mainly indicated for the treatment of type 2 diabetes