

## Will CESAR answer the adult ECMO debate?



Over the past 30 years, extracorporeal membrane oxygenation (ECMO), in both venoarterial and venovenous configuration, has become the standard of care for neonates with severe respiratory failure and for postoperative support after congenital heart repair. However, the use of ECMO in adults is not so straightforward. The ECMO experience in adults has been confined to a few highly specialised centres due to the associated expense and training necessary as well as the disappointing results reported in the only two randomised trials.<sup>1,2</sup> Recent positive anecdotal experience in hundreds of patients in Europe with the iLA system for CO<sub>2</sub> removal,<sup>3</sup> improvements in ECMO technology and management, and the many changes in critical care since the 1980s cause many to question if it is time to re-evaluate ECMO's role in the care of the severely ill adult. In *The Lancet* today, Giles Peek and colleagues present the results of the much anticipated (and debated) CESAR trial of ECMO in adults.<sup>4</sup>

This study screened 766 patients for inclusion, of whom 180 were randomised (90 to management and ECMO at Glenfield Hospital and 90 to conventional management as practised at the participating tertiary-care centres). Intent-to-treat analysis was used for survival and cost analysis. The CESAR trial showed a 16% survival benefit without severe disability for patients in the ECMO referral group over conventional management. ECMO referral therefore seems beneficial as part of an overall management algorithm in the critically ill patient compared with conventional ventilation alone. More patients in the ECMO referral group than in the control group survived, but this difference was not statistically significant (relative risk 0.73, 95% CI 0.52–1.03,  $p=0.07$ ). Three of the patients in the control group were lost to disability follow-up, reducing the group to 87. One patient in the control group was severely disabled. Five patients in the ECMO referral group died during or involving transport. A strength of the study design is the fact that the transport risk was included in the comparison. Only 68 of the 90 patients in the ECMO referral group were actually placed on ECMO; 14 of 17 survived with critical care management alone, and 43 (63%) of 68 survived to 6 months. It is important therefore to understand that the relative risk benefit reported is not for ECMO

treatment but for referral to a single ECMO-capable hospital for ECMO assessment and management if criteria are met. The single referral center, however, leads to a potential weakness of this study; possibly, improved care at the single ECMO hospital led to the relative risk observed. This point restricts the generalisability of this study; ECMO referrals to other ECMO-capable hospitals might not see the same improvements.

Survival without severe disability in patients referred for ECMO assessment was at twice the length of stay and twice the cost. Important issues include use of local conventional management rather than a standard critical-care protocol addressing diuresis, low-tidal-volume ventilation, use of steroids and antibiotics, and fluid management. As seen in several trials in acute respiratory syndrome, including the ARDSNet study,<sup>5</sup> the usual observed survival with critical-care protocol involving a low tidal volume is about 60%.

Will this trial change clinicians' opinion of adult ECMO? To clinicians who have witnessed first-hand ECMO's ability to salvage an unstable life that would presumably be lost without it, today's study will represent the sentinel paper on adult ECMO for years to come. After all, 63% of patients who were dying survived to 6 months with ECMO referral. The study involved hundreds of clinicians and years of planning in the design and execution, resulting in the largest (and best) randomised trial of adult ECMO referral so far published. Most proponents of ECMO will conclude that

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patients treated in a hospital where ECMO was a part of the algorithm fared better than patients in hospitals that did not offer ECMO. They will argue that the strengths of CESAR far outweigh the risks of transport and ECMO as well as any statistical critique.

Do the modest benefits shown in today's trial outweigh the risk? To those who question ECMO's role in adult critical care, this study will do little to change their minds. Detractors will argue that the intent-to-treat analysis and lack of protocol for ventilator and critical-care management in patients not randomised to receive ECMO weaken the conclusions. ECMO also requires a dedicated team and capital investment in equipment not standard in intensive care. The benefits observed in CESAR are unlikely to convince a centre to start an adult ECMO programme or convince a tertiary hospital to transfer critically ill patients to an ECMO centre. Critics will point out that the benefit was modest at best and non-existent if those transferred but not treated with ECMO are not included in the analysis. They will point out that the cost benefit is only directly applicable to the UK health-care system, and that the expense of training a team and maintaining equipment minimises any savings to be realised.

Ultimately, the CESAR group should be congratulated on completion of such a complex and large trial. The debate that will surround this study reflects the difficulty of this type of research in the critically ill patient. This study will likely provide ammunition for both those in favour and those against the use of ECMO in the adult population.

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We declare that we have no conflicts of interest.

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# 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<sub>2</sub>O of peak inspiratory pressure) or high FiO<sub>2</sub> ( $>0.8$ ) 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 £19252 (95% CI 7622–59200) 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%.<sup>1–6</sup> Surviving patients could have clinically significant physical (respiratory and musculoskeletal) and neuropsychological (emotional and cognitive) disabilities.<sup>3</sup> Such patients need inpatient rehabilitation and hospital readmissions, leading to high financial burden on carers and health-care systems.<sup>3</sup>

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.

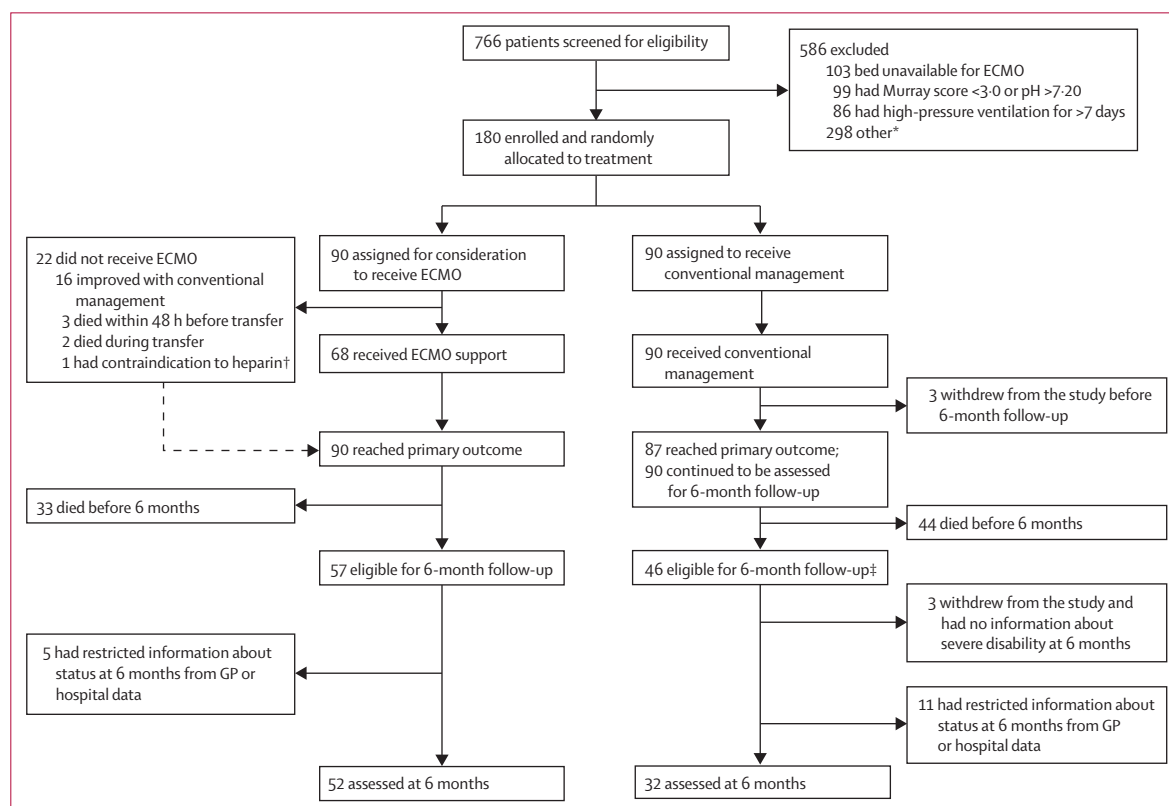
Two previous randomised controlled trials have assessed adult extracorporeal life support.<sup>7,8</sup> Neither of these studies has relevance to modern ECMO because the case selection, ventilation strategies, extracorporeal

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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%<sup>6,9</sup> compared with up to 66% with ECMO (including full support of oxygenation and lung rest).<sup>10–12</sup> 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.<sup>13</sup> 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 participating centre.

Eligible patients were aged 18–65 years with severe but potentially reversible respiratory failure, and a Murray score<sup>14</sup> (from all four variables— $\text{PaO}_2/\text{FiO}_2$  ratio, positive end-expiratory pressure, lung compliance, and chest radiograph appearance—and  $\text{FiO}_2=1$ ) 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.<sup>15</sup> 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 <sub>2</sub> , 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 <sub>2</sub> /FiO <sub>2</sub> (mm Hg <sup>-1</sup> )	75.9 (29.5)	75.0 (35.7)
Positive end-expiratory pressure (cm H <sub>2</sub> O)	13.7 (9.6)	14.2 (9.4)
Lung compliance (mL/cm H <sub>2</sub> O)	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 millitary 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 were deemed too sick to move by the transport team.

Table 2: Actual management after randomisation

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<sub>2</sub>O) or high FiO<sub>2</sub> (>0.8) ventilation.

### Study design

We designed CESAR to be a pragmatic trial, similar to the UK trial of neonatal ECMO<sup>16,17</sup> 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.<sup>13,18</sup>

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

Patients were excluded if they had: been on high pressure (peak inspiratory pressure >30 cm H<sub>2</sub>O) or high FiO<sub>2</sub> (>0.8) ventilation for more than 168 h (7 days); signs of



	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<sub>2</sub> 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.<sup>11</sup> 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.<sup>13</sup>

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,<sup>19</sup> and pressure plateau of less than 30 cm H<sub>2</sub>O. 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<sub>2</sub>O, positive end-expiratory pressure titrated to optimum SaO<sub>2</sub>, FiO<sub>2</sub> titrated to maintain SaO<sub>2</sub> 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<sub>2</sub>>90% needed to maintain SaO<sub>2</sub>>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.<sup>11,13</sup> All ECMO was done in the venovenous mode with percutaneous cannulation. Servo-controlled roller pumps (Stockert, Freiburg, Germany) and poly-methyl pentene oxygenators (Medos Medizintechnik, 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<sub>2</sub> 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.<sup>20</sup> Murray lung injury score and ratio of PaO<sub>2</sub> to FiO<sub>2</sub> 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,

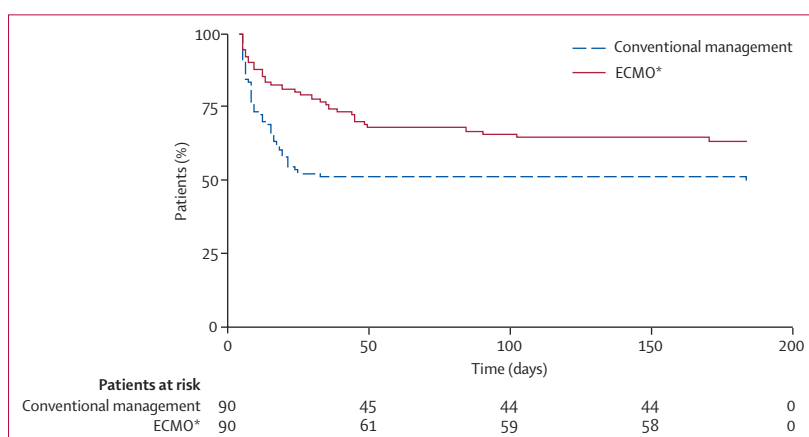
steroids), primary and secondary outcomes, and compliance with the low-volume low-pressure ventilation strategy (pressure plateau or positive inspiratory pressure less than 30 cm H<sub>2</sub>O). We collected these data for patients on ECMO, in addition to ECMO management information (cannulation, flow, 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,<sup>21</sup> EuroQol-5 dimensions (EQ-5D),<sup>22</sup> St George's hospital respiratory questionnaire,<sup>23</sup> hospital anxiety and depression scale,<sup>24</sup> and mini-mental state examination,<sup>25</sup> and specific questions were asked about sleep from the functional limitation profile.<sup>26</sup> If applicable, we measured effects on the carer using the carer strain index.<sup>27</sup> Lung function was assessed by spirometry. Upper arm movements were assessed because restriction had been noted after ECMO previously.<sup>13</sup> 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.<sup>18</sup> 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



**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)
<b>All patients</b>		
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)
<b>Patients who died‡</b>		
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**

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.<sup>28</sup> On the basis of this work and previous statistical analyses of the costs of critical care patients,<sup>29</sup> 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.<sup>30,31,32</sup> 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;<sup>33,34</sup> unit costs of care after discharge were based on the same sources.

	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%)

(Continues on next page)

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.<sup>22</sup>

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.<sup>35</sup> 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<sup>36</sup> 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;<sup>37</sup> (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;<sup>31,38–41</sup> (3) average health states for different age-groups could be obtained from the 1996 health survey for England;<sup>42</sup> 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.<sup>43</sup> 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.<sup>44</sup>

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.<sup>45</sup>

### 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  $\alpha=0.05$  (two-sided) and  $\beta=0.2$ , 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.<sup>10,11</sup> Several other scenarios were shown on a sample size grid in the



published protocol.<sup>13</sup> 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  $\chi^2$  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<sup>46</sup> and Peto's<sup>47</sup> 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

	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)
Carer/giver 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 <sub>1</sub> (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 <sub>1</sub> =forced expiratory volume in 1 s. FVC=forced vital capacity. FER=forced expiratory ratio (FEV <sub>1</sub> /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.		
<b>Table 5: Follow-up assessment at 6 months</b>		

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=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 treatment by ECMO spent longer in critical care, and in hospital, than those allocated to conventional management, especially those who ultimately died (table 4).

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<sup>18</sup> 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

See Online for webappendix

	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.<sup>48,49</sup> 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<sub>2</sub> 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.<sup>50,51</sup>

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<sup>19</sup> 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 is 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.<sup>7,8,16,52-54</sup> The influential UK neonatal ECMO trial<sup>16</sup> 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)<sup>8</sup> 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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**It support:** A King, M Bennett.

**Randomisation service:** G McPherson, A Walker.

**Independent categorization of causes of deaths:** C Waldmann, D Goldhill.

#### Participating centres

For all centres that recruited patients, we have listed each hospital with the names of collaborating medical staff. The number in brackets represents the number of patients recruited by that centre.

**Airedale General Hospital, Airedale** (2) J Scriven, K Price; **Alexandra Hospital, Redditch** (1) T Leach, D Bagnall, L Clements; **Arrowe Park Hospital, Liverpool** (1) JP Gannon, J Chambers, P Grice, C Taylor; **Ayr Hospital, Ayr** (6) I Taylor, M Dunlop, D Kerr; **Bassetlaw District General Hospital, Worksop** (1) R Harris, W Lee, P Wootton; **Bedford Hospital, Bedford** (10) D Niblett, F Barchard, F Bertasius; **Castle Hill Hospital, Cottingham** (8) S Gower, J Dickson, K Roberts; **Cheltenham General Hospital, Cheltenham** (2) W Doherty, A Culpepper, S Maisey; **Chesterfield & North Derbyshire Royal Hospital, Chesterfield** (2), RP Wroth, L Barton, D Handley; **Chorley & South Ribble District General Hospital, Chorley** (1) M Calleja, J Baldwin; **Derby Hospitals NHS Foundation Trust, Derby** (2) P Harris, K Greatorex, J Herring, L Thomas; **East Surrey Hospital, Redhill** (1) B Bray, B Keeling; **Frimley Park Hospital, Camberley** (3) L Shaikh, J Thomas; **Glan Clwyd District General Hospital, Rhyl** (1) B Tehan, L Burgoyne, K Owen; **Glenfield Hospital, Leicester** (8) R Firmin, G Peek, D Turner, L Marriot, J Morton, L Randall; **Gloucestershire Royal Hospital, Gloucester** (8) C Roberts, A Bailey, E Maggs; **Hereford County Hospital, Hereford** (1) J Hutchinson, L Davies, L Kehoe; **Huddersfield Royal Infirmary, Huddersfield** (2) J O'Riordan, S Ainley, S Maguire; **Hull Royal Infirmary, Hull** (3) I Smith, D Muir, N Smith; **Kent & Sussex Hospital, Royal Tunbridge Wells** (1) P Sigston, A Collins; **Kettering General Hospital, Kettering** (3) L Twohey, C Harland, J Thomas; **King's Mill Hospital, Sutton in Ashfield** (1) M Ross, M Platt, A Tinsley; **Leicester General Hospital,**

**Leicester** (2) P Spiers, J Cadwallader; **Leicester Royal Infirmary, Leicester** (6) D Turner, K Coulson; **Leighton Hospital, Leighton** (3) A Martin, T Schiavone, M Smith; **Llandough Hospital, Llandough** (1) A Turley, C Taylor, S Bennett, R Kyte; **Luton & Dunstable Hospital, Luton** (10), M Patten, M Kermack; **Macclesfield District General Hospital, Macclesfield** (4), J Hunter, H Cooper, J Rhodes; **Manchester Royal Infirmary, Manchester** (1) R Slater, W Cook; **Milton Keynes General Hospital, Milton Keynes** (1) P Chambers, J McHugh; **Newham University Hospital, London** (1) S Holbeck, C McMullen, L Woodbridge; **Ninewells Hospital and Medical School, Dundee** (1) JR Colvin, B Soutar; **North Manchester General Hospital, Manchester** (1) M Longshaw, E Jones; **Northern General Hospital, Sheffield** (3) S Michael, J Sutherland, L Wadsworth; **Nottingham City Hospital, Nottingham** (2) M Levitt, C Crocker, M Hope; **Pilgrim Hospital, Boston** (3) M Spittal, D Connolly, I Hamilton; **Prince Charles Hospital, Merthyr Tydfil** (1) B Jenkins, J Davies; **Prince Philip Hospital, Llanelli** (4) M Esmail, L Evans; **Queen Elizabeth Hospital, Gateshead** (6) F McAuley, E Britton-Smith, A Jackson, V McLean; **Raigmore Hospital, Aberdeen** (1) CA Lee, G Calder; **Rotherham District General Hospital, Rotherham** (2) D Harling, D O'Malley, H Proctor; **Royal Albert Edward Infirmary, Wigan** (1) R Saad, J Hilton, M Taylor; **Royal Bolton Hospital, Bolton** (4) W Price, S Westwell; **Royal Hallamshire Hospital, Sheffield** (7) D Edbrooke, K Bailey, S Smith; **Royal Liverpool University Hospital, Liverpool** (1) G Masterston, T Rowan; **Royal Preston Hospital** (1) P Duncan, C Richardson; **Sandwell General Hospital, Birmingham** (1) J M Bellin, A Markham, M Willis; **Scunthorpe General Hospital, Scunthorpe** (1) T Samuel, R Sharawi, A Holmes, S Snelson; **Southend Hospital, Southend** (1) D Higgins, J Lee, P Tyler; **Southport & Ormskirk Hospital NHS Trust, Southport** (1) D Jayson, G Levens, H Rymell, M Smith, M Vangikar, J Webb; **St Mary's Hospital, Portsmouth** (1) C Wareham, J Bean, A Read; **Staffordshire General Hospital, Stafford** (1) J Hawkins, J Lewis, N Worrall; **Stepping Hill Hospital, Stockport** (3) J Rigg, K Berry, S Swire; **Horton Hospital, Banbury** (2) J Everatt, G Walker, K Marchant; **Ipswich Hospital, Ipswich** (1) M Garfield, C Calder, M Parfitt; **Royal London Hospital, London** (4) D Kennedy, S Nourse, I O'Connor; **University Hospital Aintree, Liverpool** (1) E Shearer, P Hale, S Taberner; **University Hospital of Hartlepool, Hartlepool** (3) V Gupta, L Morgan; **University Hospital of North Staffordshire NHS Trust, Stoke on Trent** (1) B Carr, T Proctor, A Normington; **University Hospital of Wales, Cardiff** (1) G Findlay, M Smithie, E Hutcheon; **Victoria Hospital, Blackpool** (1) D Kelly, M Drummond; **Walsgrave Hospital, Coventry** (2) J Little, D Watson, T Mason, G McMillan; **Warrington Hospital, Warrington** (1) J Little, T Mason, G McMillan; **Warwick Hospital, Warwick** (5) J Aulakh, H Reading; **Watford General Hospital, Watford** (1) V Page, T Stambach, C Armstrong, W Dore; **West Suffolk Hospital, Bury St Edmunds** (4) J Cardy, P Oats, S Humphreys; **Worcestershire Royal Hospital, Worcester** (4) N Volpe; **Wrexham Maelor Hospital, Wrexham** (3) WC Edmondson, K Miller; **Wycombe Hospital, High Wycombe** (2) T Dexter, R Bryson, G Toovey.

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, Ilford;** **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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