

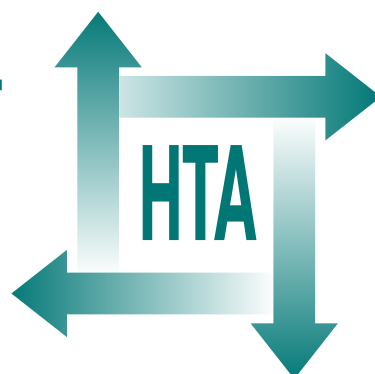
## **Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR)**

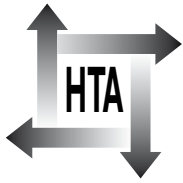
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and A Truesdale



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# Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR)

GJ Peek,<sup>1\*</sup> D Elbourne,<sup>2</sup> M Mugford,<sup>3</sup>  
R Tiruvoipati,<sup>1</sup> A Wilson,<sup>4</sup> E Allen,<sup>2</sup>  
F Clemens,<sup>2</sup> R Firmin,<sup>1</sup> P Hardy,<sup>2,5</sup>  
C Hibbert,<sup>6</sup> N Jones,<sup>1</sup> H Killer,<sup>1</sup> M Thalanany<sup>3</sup>  
and A Truesdale<sup>2</sup>

<sup>1</sup>Department of Cardiothoracic Surgery, Glenfield Hospital, Leicester, UK

<sup>2</sup>Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK

<sup>3</sup>Health Economics Group, School of Medicine Health Policy and Practice, University of East Anglia, Norwich, UK

<sup>4</sup>Department of Health Sciences, University of Leicester, UK

<sup>5</sup>Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Melbourne, Australia

<sup>6</sup>School of Health and Related Research, University of Sheffield, UK

\*Corresponding author

**Declared competing interests of authors:** GJP, RT, RF and HK and are all clinicians involved in providing ECMO services.

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## Abstract

### Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR)

GJ Peek,<sup>1\*</sup> D Elbourne,<sup>2</sup> M Mugford,<sup>3</sup> R Tiruvoipati,<sup>1</sup> A Wilson,<sup>4</sup> E Allen,<sup>2</sup> F Clemens,<sup>2</sup> R Firmin,<sup>1</sup> P Hardy,<sup>2,5</sup> C Hibbert,<sup>6</sup> N Jones,<sup>1</sup> H Killer,<sup>1</sup> M Thalanany<sup>3</sup> and A Truesdale<sup>2</sup>

<sup>1</sup>Department of Cardiothoracic Surgery, Glenfield Hospital, Leicester, UK

<sup>2</sup>Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK

<sup>3</sup>Health Economics Group, School of Medicine Health Policy and Practice, University of East Anglia, Norwich, UK

<sup>4</sup>Department of Health Sciences, University of Leicester, UK

<sup>5</sup>Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Melbourne, Australia

<sup>6</sup>School of Health and Related Research, University of Sheffield, UK

\*Corresponding author

**Objectives:** To determine the comparative effectiveness and cost-effectiveness of conventional ventilatory support versus extracorporeal membrane oxygenation (ECMO) for severe adult respiratory failure.

**Design:** A multicentre, randomised controlled trial with two arms.

**Setting:** The ECMO centre at Glenfield Hospital, Leicester, and approved conventional treatment centres and referring hospitals throughout the UK.

**Participants:** Patients aged 18–65 years with severe, but potentially reversible, respiratory failure, defined as a Murray lung injury score  $\geq 3.0$ , or uncompensated hypercapnoea with a pH  $< 7.20$  despite optimal conventional treatment.

**Interventions:** Participants were randomised to conventional management (CM) or to consideration of ECMO.

**Main outcome measures:** The primary outcome measure was death or severe disability at 6 months. Secondary outcomes included a range of hospital indices: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of intensive care unit stay, and length of hospital stay – and (for ECMO patients only) mode (venovenous/veno-arterial), duration of ECMO, blood flow and sweep flow.

**Results:** A total of 180 patients (90 in each arm) were randomised from 68 centres. Three patients in

the conventional arm did not give permission to be followed up. Of the 90 patients randomised to the ECMO arm, 68 received that treatment. ECMO was not given to three patients who died prior to transfer, two who died in transit, 16 who improved with conventional treatment given by the ECMO team and one who required amputation and could not therefore be heparinised. Ninety patients entered the CM (control) arm, three patients later withdrew and refused follow-up (meaning that they were alive), leaving 87 patients for whom primary outcome measures were available. CM consisted of any treatment deemed appropriate by the patient's intensivist with the exception of extracorporeal gas exchange. No CM patients received ECMO, although one received a form of experimental extracorporeal arteriovenous carbon dioxide removal support (a clear protocol violation). Fewer patients in the ECMO arm than in the CM arm had died or were severely disabled 6 months after randomisation, [33/90 (36.7%) versus 46/87 (52.9%) respectively]. This equated to one extra survivor for every six patients treated. Only one patient (in the CM arm) was known to be severely disabled at 6 months. Patients allocated to ECMO incurred average total costs of £73,979 compared with £33,435 for those undergoing CM (UK prices, 2005). A lifetime model predicted the cost per quality-adjusted life-year (QALY) of ECMO to be £19,252 (95% confidence interval £7622 to £59,200) at a discount rate of 3.5%. Lifetime QALYs gained were

10.75 for the ECMO group compared with 7.31 for the conventional group. Costs to patients and their relatives, including out of pocket and time costs, were higher for patients allocated to ECMO.

**Conclusions:** Compared with CM, transferring adult patients with severe but potentially reversible respiratory failure to a single centre specialising in the

treatment of severe respiratory failure for consideration of ECMO significantly increased survival without severe disability. Use of ECMO in this way is likely to be cost-effective when compared with other technologies currently competing for health resources.

**Trial registration:** Current Controlled Trials ISRCTN47279827.



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## List of abbreviations

AA	Automobile Association	MARS	Molecular Adsorbents Recirculating System
ALI	acute lung injury	NICE	National Institute for Health and Clinical Excellence
APACHE II	Acute Physiology and Chronic Health Evaluation II (score)	NIH	National Institutes of Health
ARDS	acute respiratory distress syndrome	PaO <sub>2</sub>	arterial oxygen pressure
CESAR	Conventional ventilation or ECMO for Severe Adult Respiratory failure (trial)	PCIRV	pressure controlled inverse ratio ventilation
CI	confidence interval	PEEP	positive end-expiratory pressure
CM	conventional management	PIP	peak inspiratory pressure
CTC	conventional treatment centre	QALY	quality-adjusted life-year
DMC	Data Monitoring Committee	RCT	randomised controlled trial
ECCO <sub>2</sub> R	extracorporeal carbon dioxide removal	RH	referring hospital
ECMO	extracorporeal membrane oxygenation	RR	relative risk
EQ-5D	EuroQol 5 dimensions questionnaire	SERNIP	UK Safety and Efficacy Register of the New Interventional Procedures
FiO <sub>2</sub>	fractional inspired oxygen	SF-36	Short Form (36 items)-health survey
HTA	Health Technology Assessment	SOFA	Sepsis-related Organ Failure Assessment (score)
ICU	intensive care unit	VA	veno-arterial
IQR	interquartile range	VV	venovenous
IPPV	intermittent positive pressure ventilation		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.





## Executive summary

### Background

Severe respiratory failure has a high mortality in adult patients despite recent advances in intensive care. The fundamental dichotomy of conventional treatment of these patients is that positive pressure ventilation is dangerous when high concentrations of oxygen (fractional inspired oxygen, FiO<sub>2</sub>) and large tidal volumes/high airway pressures are used, as such ventilation causes ventilator-induced lung injury, which decreases survival. The paradox is that the sickest patients with the severest lung injury require the highest ventilator settings and are most at risk of ventilator-induced lung injury. Extracorporeal membrane oxygenation (ECMO) uses cardiopulmonary bypass technology to support gas exchange in the intensive care unit (ICU) allowing ventilator settings to be reduced, thereby giving the lungs a chance to recover. Although ECMO has been proven in a randomised controlled trial (RCT) to increase survival in severe neonatal respiratory failure, its use in adults has not been similarly validated.

### Objectives and entry criteria

CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) was a nationwide UK RCT whose primary hypothesis was that ECMO will improve survival without severe disability at 6 months for adults (18–65 years) with severe (Murray lung injury score  $\geq 3.0$  or pH  $< 7.2$ ) but potentially reversible respiratory failure and will be cost-effective.

### Funding

The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme and the clinical treatment costs were funded by the NHS via the National Specialist Commissioning Advisory Group for England and Wales and through the Scottish Executive.

### Setting

One hundred and three hospitals obtained ethics committee approval to participate, and trial entry was also allowed from centres that did not have ethics committee approval as long as they agreed to transfer the patient to a centre with approval under the Emergency Inclusion Protocol.

### Contraindications

Contraindications to trial entry were high pressure/high FiO<sub>2</sub> ventilation ( $> 30$  cm H<sub>2</sub>O of peak inspiratory pressure) and/or high FiO<sub>2</sub> ( $> 0.8$ ) ventilation for more than 7 days; signs of intracranial bleeding; any other contraindication to limited heparinisation; or any contraindication to continuation of active treatment.

### Outcome measures

The primary outcome measure was death or severe disability at 6 months. Severe disability was defined as patients being unable to wash or dress themselves and confined to bed. Primary analysis was by intention to treat.

### Patients and methods

Between July 2001 and August 2006 enquiries were made about 766 potentially eligible patients from 148 centres. One hundred and eighty of these were randomised from 68 centres, 90 in each arm. Patients were randomised via a telephone call to an automated independent central randomisation service either to continued conventional treatment or to transfer to Glenfield Hospital in Leicester for consideration of ECMO; to ensure close balance between treatment groups for minimisation was used. After the first patient was allocated treatment using simple randomisation, the next patient to enter the trial was allocated to whichever treatment group improved the overall balance according to a pre-selected set of baseline minimisation criteria,

namely type of centre [conventional treatment centre (CTC) or referral hospital (RH)]; age (18–30, 31–45, 46–65 years); hours of high pressure and/or high  $\text{FiO}_2$  ventilation (0–48, 49–168); mode of trial entry (i.e. hypoxic/hypercarbic); diagnostic group [pneumonia, obstetric acute respiratory distress syndrome (ARDS), trauma including surgery within previous 24 hours, other ARDS, and other]; and numbers of organs failed (one or two, or three or more) where organ failure was a Sepsis-related Organ Failure Assessment (SOFA) score for that organ of greater than 2. If the patients were randomised to conventional management (CM) and were in a CTC, they remained in the CTC. CTCs were large ICUs that were felt by the local ICU network lead to provide all necessary treatment modalities or, where local ICU networks did not exist, were those units with more than 350 admissions per year that could provide pressure controlled ventilation and haemofiltration. Smaller hospitals that did not fulfil these criteria were classified as RHs. One hundred and forty-eight patients entered the trial from CTCs and 32 from RHs, which included patients entering under the Emergency Inclusion Protocol. If a patient in an RH drew conventional treatment they were transferred by the ECMO transport team to the nearest CTC with a bed available. All patients who drew ECMO were transferred by the same team to Glenfield Hospital for consideration of ECMO. The mean (standard deviation, SD) age at trial entry was 39.9 (13.4) years in the ECMO arm and 40.4 (13.4) years in the CM arm. Primary diagnosis at trial entry was (ECMO/CM) pneumonia 56/53, other ARDS 25/26, trauma or surgery within 24 hours 5/7 and other 4/4. The number of organs failed was (ECMO/CM) one or two in 62/63 patients and more than three in 28/27 patients. Median (interquartile range) duration of ventilation was 35.0 (17.3–104.5) hours in the ECMO arm and 37.0 (15.5–101.5) hours in the CM arm, 28.5 (17.0–69.3) of these hours were at high pressure/high  $\text{FiO}_2$  in the ECMO arm and 28.0 (12.0–88.0) in the CM arm. Eighty-five patients entered the ECMO arm for hypoxia (Murray score  $\geq 3.0$ ) and 87 entered the conventional arm, the remainder entered because of hypercarbia ( $\text{pH} < 7.2$ ). The mean (SD) Murray score was (ECMO/CM) 3.5 (0.6)/3.4 (0.3). The median (IQR) arterial oxygen pressure ( $\text{PaO}_2$ )/ $\text{FiO}_2$  ratio (ECMO/CM) was 73 (57.5–87)/70.5 (60–88) mmHg. All 85 patients in the ECMO arm who entered because of hypoxia fulfilled the American–European consensus definition of ARDS. In the conventional arm, 87 patients entered based on hypoxia, 84 fulfilled the ARDS criteria and two the acute lung injury criteria.

## Results

Of the 90 patients randomised to the ECMO arm, 68 received that treatment. ECMO was not given to three patients who died prior to transfer, two who died in transit, 16 who improved with conventional treatment given by the ECMO team and one who required amputation and could not therefore be heparinised. Ninety patients entered the CM (control) arm, three patients later withdrew and refused follow-up (meaning that they were alive), leaving 87 patients for whom primary outcome measures were available. CM consisted of any treatment deemed appropriate by the patient's intensivist with the exception of extracorporeal gas exchange. The low volume ventilation strategy from the ARDS Network (ARDSNet) study was recommended. No CM patients received ECMO, although one received a form of experimental extracorporeal arteriovenous carbon dioxide removal support (a clear protocol violation). Fewer patients in the ECMO arm than in the CM arm had died or were severely disabled 6 months after randomisation, [33/90 (36.7%) versus 46/87 (52.9%) respectively; relative risk (RR) = 0.69 [95% confidence interval (CI) 0.50 to 0.97];  $p = 0.030$ ]. This equated to one extra survivor for every six patients treated. Only one patient (in the CM arm) was known to be severely disabled at 6 months.

## Economic evaluation

Previous studies of ECMO had not estimated the additional costs or the consequences of treatment. However, the high costs of intensive care and changes in resource use and quality of life resulting from changes in clinical outcome suggested the potential for ECMO treatment to have an important economic impact in the NHS. Full economic evaluation was therefore built into the CESAR trial. The economic data collection and economic analysis took the perspectives of the NHS and of the household.

Data about resource use and economic outcomes [quality-adjusted life-years (QALYs)], were collected from participating patients. Estimated QALYs were based on EuroQol 5 dimensions (EQ-5D) responses at 6 months and were weighted using UK population values for health states. Studies of the key cost-generating events were undertaken, and analyses of cost–utility at 6 months post randomisation and modelled lifetime cost–utility were performed.

Lifetime QALYs were estimated based on the assumption that the quality of life of all surviving patients improved up to 24 months from randomisation, and that at 24 months their health states were the same as those of other adults of similar age and gender in the UK population. It was also assumed that all survivors had the same average life expectancy as adults of similar age and gender in the UK population. This assumption was based on our experience of long-term follow-up of patients who had been previously treated with ECMO.

Patients allocated to ECMO incurred average total costs of £73,979 compared with £33,435 for those undergoing CM (UK prices, 2005). At 6 months post randomisation, the additional cost of a survivor without severe disability of ECMO compared with CM was £251,360. ECMO treatment resulted in 0.03 predicted additional QALYs at 6 months' follow-up. A lifetime model predicted the cost per QALY of ECMO to be £19,252 (95% CI £7622 to £59,200) at a discount rate of 3.5%. Lifetime QALYs gained were 10.75 for the ECMO group compared with 7.31 for the conventional group.

Costs to patients and their relatives, including out of pocket and time costs, were higher for patients allocated to ECMO.

## Conclusions

A major limitation of this study is the lack of standardisation of care in the conventional arm. This was because it was not possible for the

conventional intensive care providers to reach a consensus as to what constituted optimal care. An alternative strategy of transferring all the patients to Glenfield to be cared for by the ECMO team was dismissed by collaborators as they did not consider the ECMO team to be sufficiently expert in the provision of conventional intensive care. The other possibility considered was to use a single centre to provide all of the conventional care, but this was impossible as such a centre does not exist in the UK. The trial team therefore took the pragmatic decision to recommend what was proven to be the best ventilation strategy (the low volume ARDSNet protocol) but allow individual intensivists to determine what they thought was the best treatment for their patients. If this decision had not been taken then it would not have been possible to conduct the study. This pragmatic design meant that CESAR was comparing treatment in an expert centre where ECMO was part of the treatment algorithm with the treatment available to the general public in the UK as a whole. Compared with CM, transferring adult patients with severe but potentially reversible respiratory failure to a single centre specialising in the treatment of severe respiratory failure for consideration of ECMO significantly increased survival without severe disability. Use of ECMO in this way is likely to be cost-effective when compared with other technologies currently competing for health resources.

## Trial registration

This trial is registered as ISRCTN47279827.



# Chapter I

## Introduction

The mortality rate for adults with severe respiratory failure is very high and has improved only marginally in the majority of centres over the last 20 years.<sup>1,2</sup> As there may be as many as 350 adult patients with severe, but potentially reversible, respiratory failure in the UK each year, this is a significant problem. Current management uses intermittent positive pressure ventilation (IPPV). The airway pressures and oxygen concentrations required to maintain adequate blood gases are often very high in patients with severe respiratory failure, and this combination of barotrauma, volutrauma and oxygen toxicity can prevent lung recovery. The only type of ventilation that has been proven in a randomised controlled trial (RCT) to improve outcome in adults with moderate, but potentially reversible, respiratory failure is the use of gentle lung protective ventilation.<sup>4</sup> Unfortunately patients with severe, but potentially reversible, respiratory failure have such bad lung disease that they are unable to maintain homeostasis if such lung protective ventilation is used. Ironically, these are the very patients who need lung protective ventilation the most. An alternative treatment, extracorporeal membrane oxygenation (ECMO), uses cardiopulmonary bypass technology to temporarily provide gas exchange to patients with severe, but potentially reversible, respiratory failure. During ECMO, ventilator settings can be reduced, and 'lung rest' achieved, thereby allowing the lungs to recover. There is currently no good evidence from RCTs to compare ECMO with conventional management (CM) for important clinical outcomes.

Patients are usually considered for ECMO when they have such severe disease that they continue to deteriorate despite maximal optimum 'conventional' treatment. For the purposes of this discussion, 'conventional' will be defined as any treatment that relies on the patient's lungs to provide gas exchange. Conventional treatment therefore includes ventilation with inhaled nitric oxide, prone ventilation<sup>4-6</sup> and high frequency oscillation,<sup>7</sup> as well as the more usual types of positive pressure ventilation. ECMO has been proven to increase survival in *neonatal* patients with severe respiratory failure in a rigorous RCT.<sup>8,9</sup>

This UK collaborative neonatal ECMO RCT convincingly demonstrated the effectiveness of ECMO in improving patient survival without severe disability. Neonatal ECMO in the UK is now a supra-regional service receiving central funding. The use of ECMO as it is currently practised in older children<sup>10</sup> and adults<sup>11</sup> is more controversial, and has yet to be evaluated in an RCT in the UK.

### Previous studies

A review of the literature was carried out to identify all studies relevant to adult ECMO. MEDLINE was searched using 'adult', extracorporeal life support (ECLS) and 'ECMO' as keywords. In addition the investigators are closely aware of the ECMO literature, as they are leading members of the international ECMO community. Only two RCTs have been reported,<sup>1,12</sup> both from the USA, but they used such different approaches that they have not been combined as a formal meta-analysis. Neither of these studies investigated high flow venovenous (VV) ECMO, which is the current technique of choice for adult respiratory failure. Each study is detailed below, followed by the recent non-experimental evidence.

The first study was an RCT of adult ECMO, conducted by the US National Institutes of Health (NIH),<sup>1</sup> in the early days of extracorporeal support in the 1970s. Survival in both groups was very poor (around 10%), and no difference was shown in survival between the conventional and ECMO treated groups. Only very small numbers of patients were treated in each centre (fewer than five). There were a number of important differences in the perfusion and ventilation techniques used during this trial compared with those used today. Firstly, veno-arterial (VA) rather than VV perfusion was used, and this was thought to be responsible for the high incidence of pulmonary micro-thrombosis and fibrosis seen in the lungs of the ECMO patients (due to reduced pulmonary blood flow). Secondly, patients were anticoagulated to such a degree that severe bleeding occurred. Thirdly, high pressure ventilation was continued during ECMO,

resulting in continued ventilator lung injury with barotrauma and volutrauma.<sup>13,14</sup> Finally, the mean duration of ventilation prior to ECMO in the NIH ECMO trial was more than 9 days, whereas it is now well recognised that after 7 days of high pressure ventilation with high fraction of inspired oxygen ( $\text{FiO}_2$ ), the lungs have limited powers of recovery.<sup>15</sup>

The second RCT was more recent, and concerned the related technique of extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R).<sup>12</sup> This showed no difference between ECCO<sub>2</sub>R and conventional treatment. Again there were numerous differences in the clinical and perfusion protocols between this trial and those in widespread use in the majority of centres currently.<sup>16,17</sup> Firstly, the experimental arm of the trial used low flow ECCO<sub>2</sub>R in a group of patients who had severe lung disease, which warranted higher flow ECMO with full support of oxygenation and carbon dioxide removal. This was demonstrated by the need to increase the airway pressure in the ECCO<sub>2</sub>R group halfway through the study. The reliance on the patient's lungs to provide oxygenation, especially at such high airway pressures, also eliminated any possibility of lung rest. Also, despite the involvement of one of the team in the 1970s NIH ECMO trial, the ECCO<sub>2</sub>R programme in this trial was not well developed prior to the study (as the team had only provided ECCO<sub>2</sub>R to sheep and one patient before starting the trial). The high incidence of bleeding and thrombotic complications reported in this study may attest to this inexperience. In addition, the conventional treatment used in the trial was pressure controlled inverse ratio ventilation (PCIRV) using a computer-controlled algorithm. The results of this treatment showed a 44% survival rate compared with expected survival rates of less than 20% in other similar series of patients.<sup>2</sup> Despite this, the survival rate in the ECCO<sub>2</sub>R group was the same as in the 'conventional' group. The success of the PCIRV protocol in this study has led to the wide adoption of the technique within 'conventional' ventilatory management with a survival rate of 66% for patients with *moderate to severe* respiratory failure [mean Murray lung injury score 2.8, mean ratio between the oxygen tension in the arterial blood and the fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) 88 mmHg].<sup>18</sup> Unfortunately no other authors have been able to duplicate the PCIRV results of Morris *et al.*<sup>12</sup> for patients with *severe progressive* respiratory failure.

Because the two trials described above have little relevance to the high flow VV ECMO regimens used in the majority of centres worldwide, the only

relevant evidence consists of observational studies. By the nature of their design, the information they provide is potentially biased, and must therefore be viewed with caution.

Recent case series of patients with similar degrees of respiratory failure to the eligibility criteria for the second trial suggest survival rates with conventional ventilation of 33–44%<sup>19,20</sup> compared with rates of up to 66% with high flow ECMO (including full support of oxygenation and lung rest), provided by experienced teams principally in the USA, UK and Germany.<sup>11,15–17</sup>

In a cohort study of the first 50 adult patients to receive ECMO for respiratory support at Glenfield Hospital, Leicester, UK, patients had severe respiratory failure as shown by the mean pre-ECMO Murray score of 3.4 [standard deviation (SD) 0.5] and  $\text{PaO}_2/\text{FiO}_2$  ratio of 65 mmHg (SD 36.9). They were referred for ECMO with severe respiratory failure caused by either the acute respiratory distress syndrome (ARDS) or pneumonia. The overall survival rate was 66%.<sup>11</sup>

For the reasons outlined above, it was impossible to reach firm conclusions from the above experimental and observational data regarding the clinical effectiveness or cost-effectiveness of VV high flow ECMO for respiratory failure in adults without an RCT.

ECMO received a Cii categorisation (safety and/or efficacy not yet fully established; procedure requires a fully controlled evaluation) from the UK Safety and Efficacy Register of the New Interventional Procedures of the Medical Royal Colleges (SERNIP). During the study SERNIP was superseded by the National Institute for Clinical Excellence (NICE; now known as the National Institute for Health and Clinical Excellence) which issued the following guidance in January 2004: 'ECMO in adults is under evaluation in the Health Technology Assessment Programme's CESAR (Conventional Ventilation or Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial. Clinicians wishing to undertake this procedure are strongly advised to enter eligible patients into this trial.'

## Economics of ECMO

Given the high cost of treatment, ECMO is considered an expensive technology for many funding systems. However, conventional treatment

for severe respiratory failure is also one of the more costly forms of care in any health system.<sup>21</sup> Differences in lengths of stay and types of care received by patients following either clinical pathway may result in different statistical distributions of cost for inpatient care. Also, because appropriate care is provided in relatively few centres, the location of care and need for specialist transport for patients also affects the costs of care. Moreover, if there is increased survival to discharge from hospital, then there will be more use of services in primary and community care, and requirement for help for people recovering at home. Thus the health service costs and the household costs might fall at any stage of the treatment and recovery, and in many different forms. In addition to the costs of alternative forms of care, the economic choice depends on the value of the outcome gained.

### Previous economic evaluations

A literature search failed to find any economic evaluation studies of adult ECMO. However, there has been a series of economic evaluations of ECMO in babies alongside the UK collaborative randomised trial of neonatal ECMO,<sup>22</sup> which reported the estimated additional cost (UK 1994–5

price) of ECMO per additional surviving infant with no disability as £75,327 at 1 year of age. Follow-up at 4 and 7 years for the same study shows the incremental cost (UK 2001 and 2003 prices) of neonatal ECMO to be £24,775 and £23,566 per disability-free life-year gained respectively.<sup>23,24</sup> Similarly, a retrospective cost–utility analysis of ECMO in children<sup>25</sup> reports costs of US \$24,386 per quality-adjusted life-year (QALY) saved for ‘salvage ECMO’. In all cases, in spite of the high cost of ECMO, the incremental cost per QALY was within health-care funders’ range of acceptable value for money.

For the reasons outlined above, it is impossible to reach firm conclusions from the above experimental and observational data regarding the clinical effectiveness or cost-effectiveness of VV high flow ECMO for respiratory failure in adults. The aim of the CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) trial was therefore to assess whether for patients with severe, but potentially reversible, respiratory failure, ECMO would increase the rate of survival without severe disability by 6 months post randomisation and would be cost-effective from the viewpoints of the UK NHS and society, compared with conventional ventilatory support.



## Chapter 2

# Methods

CESAR was a 'pragmatic' RCT, similar to the UK neonatal ECMO RCT,<sup>8,9</sup> mirroring usual practice in the UK. For patients with severe, but potentially reversible, respiratory failure, the primary hypotheses were that ECMO would increase survival without severe disability by 6 months post randomisation compared with conventional ventilation, and be cost-effective from the viewpoints of the NHS and society. Severe disability was defined as being unable to wash or dress oneself and being confined to bed.

The clinical and economic protocols have been published previously and can be found in Appendices 3 and 4.

Three types of centre were included: (1) the ECMO centre at Glenfield Hospital, Leicester; (2) conventional treatment centres (CTCs); and (3) referring hospitals (RHs). Intensive care units (ICUs) in the UK were beginning to be formed into collaborative local critical care networks as the CESAR trial started. Where networks had been established, CTCs were defined as those centres acknowledged by the network leads to provide an appropriately high standard of conventional care. In the absence of this classification, the criteria for admission of more than 350 patients per year and provision of pressure controlled ventilation and VV haemofiltration were used as markers of sufficiently large units. RHs were non-CTCs that could enter patients into the trial, if they were prepared to transfer the patient to a CTC should the allocation be to CM. It is not standard practice in the UK to transfer patients between ICUs for treatment of respiratory failure.

One hundred and three hospitals obtained ethics committee approval to collaborate in the study, of which 92 were CTCs and 11 were RHs.

Patients could be entered into the trial if aged 18–65 years with severe but potentially reversible respiratory failure, defined as a Murray score (using all four parameters and  $\text{FiO}_2 = 1$ )<sup>26</sup>  $\geq 3.0$ , or uncompensated hypercapnoea with a  $\text{pH} < 7.20$  despite optimal conventional treatment. Reversibility was based on the clinical opinion of

one of three duty ECMO consultants (RK Firmin, GJ Peek and AW Sosnowski). The criteria for case selection have been previously discussed.<sup>27</sup> Trial registration could also be discussed when the Murray score was  $\geq 2.5$ . If the patient then continued to deteriorate, this prior discussion could expedite trial entry.

Patients were excluded if they had been on high pressure (peak inspiratory pressure  $> 30 \text{ cmH}_2\text{O}$ ) and/or high  $\text{FiO}_2$  ( $> 0.8$ ) ventilation for more than 7 days (168 hours); had signs of intracranial bleeding; had any other contraindication to limited heparinisation; or had any contraindication to continuation of active treatment. Ventilation parameters were assessed on an hourly basis: a patient would count as having had an hour of high pressure or high  $\text{FiO}_2$  ventilation if they had either a peak airway pressure above  $30 \text{ cmH}_2\text{O}$  or an  $\text{FiO}_2$  above 0.8.

### Allocation of patients

The referring intensivist contacted the advisory team at Glenfield to confirm eligibility and bed availability. He or she then discussed the trial with the patient's relative(s), gave written information (see Appendices 1 and 2), and asked for agreement to trial entry and obtained assent from the next of kin (once patients had recovered sufficiently they were told that they had been entered into a clinical trial and were given the opportunity to withdraw; three patients in the conventional arm declined further involvement in the study at this point). The advisor then telephoned the independent central randomisation service (see Appendix 2). Randomisation was to CM or to consideration of ECMO.

To ensure close balance between treatment groups for several patient factors, a dynamic process (minimisation) was used, which took into account the characteristics of the patients already entered into the trial. After the first patient was allocated treatment using simple randomisation, the next patient to enter the trial was allocated to whichever treatment group improved the overall

balance according to a pre-selected set of baseline minimisation criteria, namely type of centre (CTC or RH); age (18–30, 31–45, 46–65 years); hours of high pressure and/or high FiO<sub>2</sub> ventilation (0–48, 49–168); mode of trial entry (i.e. hypoxic/hypercarbic); diagnostic group (pneumonia, obstetric ARDS, trauma including surgery within previous 24 hours, other ARDS, and other); and numbers of organs failed (one or two, or three or more) where organ failure was a Sepsis-related Organ Failure Assessment (SOFA) score for that organ of  $\geq 2$ .<sup>28,29</sup> After 40% of recruitment had been completed, an additional step was incorporated such that if four successive randomisations for the same centre had the same allocation, the next allocation was to the other treatment. To protect allocation concealment, this amendment was not revealed to the participating centres.

## Emergency Inclusion Protocol

During the trial, ECMO was not available to eligible patients outside the study. If a hospital from outside the study wished to refer a patient, the ECMO transport team went to the hospital to assess the patient and, if appropriate and assent was obtained, to assume responsibility for the clinical care. The patient was then randomised. If the patient drew CM, the ECMO team transported the patient to the nearest available CTC, and if randomised for ECMO, they transported the patient to Glenfield.

## Interventions

### Conventional management

This was the intensive care provided as standard at each CTC. This could include any treatment prescribed by the intensivist (excluding extracorporeal gas exchange). A low volume ventilation strategy was recommended, i.e. tidal volume 4–8 ml/kg of body weight.<sup>3</sup> We defined adherence as a plateau pressure  $< 30$  cmH<sub>2</sub>O (or if plateau pressure was not measured, the peak inspiratory pressure). Patients could not be ‘crossed over’ to receive ECMO.

### ECMO

Patients randomised to ECMO were transferred to Glenfield for consideration of ECMO. Treatment was according to published institutional protocols. Patients who could be stabilised on lung protective ventilation were treated without ECMO (see below). Patients who were unstable or who required high pressure/high FiO<sub>2</sub> ventilation received VV ECMO

via percutaneous cannulation. The ECMO circuit used bladder-box servo-regulation, Stockert Roller<sup>®</sup> pumps (Stockert, Freiburg, Germany) with Tygon S-65-HL<sup>®</sup> (Norton Performance Plastics, St Gobain, Akron, Ohio, USA) raceway tubing and one or two (depending on body weight) Medos Hi-Lite 7000<sup>®</sup> membrane oxygenators (Medos, Stollberg, Germany) with 100% O<sub>2</sub> as the sweep gas. Partial anticoagulation was maintained with heparin titrated to give an activated clotting time (Actalysate, Max-ACT; Helena, Beaumont, Texas, USA) of 140–200 seconds. On ECMO, lung rest was achieved by reducing ventilation to peak inspiratory pressure (PIP) of 20–25 cmH<sub>2</sub>O, positive end-expiratory pressure (PEEP) of 10–15 cmH<sub>2</sub>O, rate of 10, duration of inspiration to duration of expiration (I:E) ratio of 1:1, and FiO<sub>2</sub> of 30% in pressure control mode using Siemens Servo 300<sup>®</sup> ventilators (Siemens, Solna, Sweden). Patients were fed appropriately and diuresed to dry weight. Haemoglobin was maintained at 14 g/dl. Steroids were given to patients with severe sepsis who had a random cortisol concentration of  $\leq 414$  nmol/l<sup>30</sup> and also to patients who had non-recovery of lung function. Patients were weaned from ECMO and decannulated when chest radiograph appearance and lung compliance improved and adequate gas exchange without excessive ventilation had returned: in general this meant a peak airway pressure  $< 30$  cmH<sub>2</sub>O and an FiO<sub>2</sub>  $< 0.6$ , to give an arterial carbon dioxide pressure (PaCO<sub>2</sub>)  $< 6$  KPa and a PaO<sub>2</sub>  $> 10$  KPa. Patients who did not receive ECMO could be managed with ventilator settings given above. These were usually patients who were volume overloaded and responded to diuresis with a rapid diminution in airway pressure and FiO<sub>2</sub>. Patients developing liver failure (bilirubin  $> 200$   $\mu$ mol/l) were supported with MARS<sup>®</sup> (Molecular Adsorbents Recirculating System, Gambro AB, Stockholm, Sweden).<sup>31</sup> The full Glenfield Hospital ECMO programme treatment protocol can be found in Appendix 5.

The ECMO circuit was constantly managed by a trained ECMO specialist nurse, in addition to the patient’s intensive care nurse. If the patient’s condition altered such that ECMO was no longer appropriate, it was not used.

### Transport

All inward transport was provided by the ECMO team. If the team decided that it was not safe to move the patient, then he or she remained in the original unit until considered safe to transfer, recovered or died.

## Outcome measures

The primary outcome measure was death or severe disability at 6 months [defined as death by 6 months or before discharge from hospital at any time to end of data collection, or where the answer to the first two questions of the EuroQol 5 dimensions questionnaire (EQ-5D) were 'confined to bed' and 'unable to wash or dress yourself', i.e. the worst possible scores for the domains for self-care and for mobility].

The secondary outcomes included a range of hospital indices: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of ICU stay, and length of hospital stay – and (for ECMO patients only) mode (VV/VA), duration of ECMO, blood flow and sweep flow.

Death of patients in the trial was recorded during the period of follow-up whenever it occurred. Staff at the CESAR trial data management centre maintained contact with all centres that had patients being treated within the CESAR trial, thus ensuring complete reporting.

In addition, health status at 6 months after randomisation was assessed in terms of activities of daily living, quality of life, respiratory symptoms, cognitive psychological state and lung function.

## Six-month follow-up

This was performed by trained researchers blinded to the random allocation in the patients' homes. Patients and their relatives were instructed not to reveal which treatment was used (see Appendices 1 and 2). A special scarf covered the neck, masking cannulation status. The assessment included SF-36 [Short Form (36 items) health survey],<sup>32</sup> EQ-5D,<sup>33</sup> St George's Hospital Respiratory Questionnaire,<sup>34</sup> Hospital Anxiety and Depression Scale<sup>35</sup> and Mini-Mental State Examination,<sup>36</sup> as well as specific sleep questions from the functional limitation profile.<sup>37</sup> Where applicable, effects on the carer were measured using the carer strain index.<sup>38</sup> Lung function was assessed by spirometry. Upper arm movements were assessed, as restriction of these has been previously noted in patients following ECMO.<sup>39</sup> If a patient was still in hospital, a modified assessment was carried out there. If a home visit was unacceptable, patients were offered a telephone interview or postal questionnaire. For those refusing this, permission was requested

for information to be sought from their general practitioner.

## Sample size

Seventy per cent mortality in the control group was anticipated when carrying out the initial power calculations in 1998/9, based on patients with similar PaO<sub>2</sub>/FiO<sub>2</sub> ratio in the NIH ARDS network database (RH Bartlett, University of Michigan, USA, 1999, personal communication), confirmed by the Case Mix Programme (Intensive Care National Audit & Research Centre, ICNARC) database, in which the mortality of the 1506 patients whose PaO<sub>2</sub>/FiO<sub>2</sub> ratio was ≤ 100 mmHg was 61.6%. The mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio of the ECMO patients<sup>11</sup> was 65 mmHg (SD 37 mmHg). Assuming a 10% risk of severe disability among survivors in both arms, alpha = 0.05 (two-sided test) and beta = 0.2, 120 patients would be required in each group (i.e. 240 in total) to detect a reduction in the rate of primary outcome by a quarter from 73% to 55%, a conservative estimate based on the descriptive studies of adult ECMO already discussed. A number of other scenarios were shown on a sample size grid in the published clinical protocol<sup>39</sup> (see Appendix 3). For example, the same size sample could detect a reduction by a third if the primary outcome rate in the control group was about 57%. The sample size was reviewed in June 2003 by the independent Data Monitoring Committee (DMC) when recruitment was running at less than 60% of its target. As the primary outcome rate in the control group was then 67%, it was agreed that a lower sample size (180 patients) would be sufficient to allow detection of reduction by a third and the HTA programme agreed an extension of the funding period to allow recruitment of 180 patients.

## Statistical analysis

Primary analyses were by intention to treat. Secondary analyses included subgroup analyses, based on the minimisation criteria at trial entry, and a per protocol analysis. The DMC reviewed interim analyses in strict confidence on seven occasions. They were charged with informing the Trial Steering Committee if there was proof beyond reasonable doubt (based on the Peto–Haybittle stopping guidelines)<sup>40,41</sup> that the data indicated that any part of the protocol under investigation was either clearly indicated or contraindicated (either for all patients or for a particular subgroup), or

it was evident that no clear outcome would be obtained with the current trial design. Except for those who supplied the confidential information, everyone (including the Trial Steering Committee, funders, collaborators and administrative staff) remained ignorant of the results of the interim analysis.

## Ethical considerations

The trial was approved by the Trent Multicentre Research Ethics Committee (MREC) as well as relevant Local Research Ethics Committees (LRECs).

## Economics methods

### Design of the economic evaluation alongside the CESAR trial

The primary objective of the economic evaluation was to assess incremental cost-effectiveness of ECMO, in terms of the incremental costs of additional survival with and without disability at 6 months post randomisation, compared with conventional treatment for severe respiratory failure. The evaluation set out to assess the cost of treatment to the health and social services and to patients and their families in each treatment group. The design of the economic evaluation was based on published recommendations for best practice.<sup>42</sup> These involve defining: the type of economic evaluation to be conducted; the comparator form of care; the perspective of the study and time horizon for costs and outcomes; appropriate outcome measures for each perspective and type of evaluation; identification, measurement and valuation of resources; estimation of unit costs; and a plan for economic analysis, which includes decisions on discounting future costs and consequences, tackling uncertainties and, finally, the presentation of results.

The objectives of the economic evaluation were:

1. To compare the costs of a policy of referral for ECMO with those of conventional treatment.
2. To assess the cost-effectiveness of referral for ECMO compared with conventional treatment in terms of additional survival with and without disability at 6 months post randomisation.
3. To assess the cost-utility of referral for ECMO compared with conventional treatment in terms of utility gain as measured by EQ-5D at 6 months' follow-up.
4. To assess the cost-utility of referral for ECMO compared with conventional treatment in terms of utility gain as measured by EQ-5D, and other sources, over a predicted lifetime.

## Type of economic evaluation

The first two analyses were planned to cover only the 6-month period from randomisation for which the CESAR trial collected data from patients. The first planned analysis was a cost-effectiveness analysis with increase in survival without severe disability at 6 months (the primary outcome in the CESAR trial) as the main outcome measure. A short-term cost-utility analysis was planned, in which health benefits would be quantified in terms of QALYs measured using the instrument EQ-5D at 6 months. Lifetime cost-utility analysis was modelled using a decision model based on CESAR trial results and including additional data for predicted lifetime QALYs and health-care costs.

## Comparator

The ideal comparator for any economic evaluation designed to assess the cost-effectiveness in a particular context is the most commonly used treatment for the condition in that context. The CESAR trial was designed as a pragmatic comparison, in which patients allocated to conventional care were receiving treatment that would be the normal form of care in the NHS. To ensure that the patients in the control group received as near as possible the best practice of care, the CESAR trial protocol specified aspects of service provision that had to be considered, including facilities available at the participating ICUs, experience of treating such patients, and certain aspects of the clinical treatment protocol for ventilated patients.<sup>39</sup> In general, however, the comparator group was intended to be representative of NHS care provision (in qualifying ICUs) for severe but potentially reversible respiratory failure during the period of the trial.

## Perspective or viewpoint for analyses

In the UK, NICE proposes that applicants presenting economic analyses for NICE appraisals should adopt an NHS perspective.<sup>43</sup> However, there are aspects of public patient choice and valuation that may not be considered in such an analysis. Economic evaluators are guided to take a societal viewpoint if possible.<sup>42</sup> As the ECMO technology may be adopted for review by NICE or a similar agency in the UK, it was decided that

the perspective for the CESAR trial should include both the NHS and societal perspectives. The latter viewpoint is important, as the results of this study are likely to have economic impacts other than through health-care requirements if there is significantly increased survival of either able-bodied or disabled adults. It was also anticipated that the results of the trial may provide useful information for a wider international audience where different ranges of services are provided within the health system.

### **Time horizon for economic evaluation**

The duration of follow-up in the CESAR trial was 6 months. This did not allow the full long-term cost and benefits to be measured. However, it satisfied the recommendation of the American Thoracic Society for cost-effectiveness analyses of ICU therapies to have a minimum follow-up period of 6 months.<sup>21</sup> However, to meet our fourth objective, prediction and modelling of long-term (lifetime) costs and benefits were also undertaken.

### **Outcome measures for economic evaluation**

#### ***Survival without severe disability***

The cost-effectiveness analysis focused on the primary outcome measure for the CESAR trial.

#### ***Quality-adjusted life-years***

The calculation of QALYs was based on assessment of health-related quality of life at 6 months from randomisation. The EQ-5D is a standardised instrument used for measuring health outcomes. The part of the EQ-5D questionnaire used to elicit health status comprises five questions, each of which has three alternative response categories. The five items assess mobility, self-care, usual activity, pain/discomfort and anxiety/depression. These items can be used by themselves as descriptions of respondents' health states. Responses were also scored by means of weights obtained from the valuations that other samples from the general population have assigned to health states using visual analogue scales. Quality-adjusted health utility weights for each patient were calculated for the CESAR trial using UK specific utility values for each patient's response to the EQ-5D at 6 months. QALYs gained at 6 months were estimated assuming that the value of the health state at trial entry was zero and that, over the months of survival, patients experienced linearly increasing quality of life up to the level at 6 months.

Estimates of lifetime QALYs were predicted based on assumptions of gradual improvement of quality of life up to 2 years from randomisation, and of predicted life expectancy based on age specific rates for the population of England and Wales. Age and sex specific life expectancy was calculated for each surviving patient in the trial using UK life tables.<sup>44</sup> It was assumed that, at 24 months post randomisation, all surviving trial patients attained the same average life expectancy and health state as adults of similar age in the UK population.<sup>45–49</sup> It was assumed that average health states for different age groups would be the same as those obtained from the 1996 Health Survey for England.<sup>50</sup> This assumption was based on our experience of long-term follow-up of patients who had been previously treated with ECMO.

### **Cost estimation**

#### ***Identifying resource use***

For the CESAR trial, relevant aspects of resource use were identified using expert advice (managers and medical, nursing and patient representatives all commented on the draft lists) and considering the items included in the economic evaluation of neonatal ECMO.<sup>22</sup> A list of resource items important from one or more viewpoints is given in *Table 1*.

This includes resource use associated with initial stay in intensive and high-dependency care units at different levels of care (measured by number of organs supported – see below), use of ambulance transport, stays in other hospital wards before discharge, costs of visiting incurred by relatives whilst patients are in hospital, resource use after discharge up to 6 months, major changes in household, out of pocket expenses of patient and family, loss of paid and unpaid working time, changes in working time, and informal care.

### **Measuring resource use**

In the CESAR trial, resource use data were collected prospectively for every trial participant at various points of his or her progress, from recruitment to the trial until follow-up, using a series of data forms and questionnaires. Some, but not all, of these were additional to the instruments used for the CESAR trial management and clinical outcome data collection.<sup>39</sup> These instruments are:

- (a) Daily organ support form – completed by critical care unit staff for each trial participant on a daily basis, and used to classify intensity

TABLE 1 Items of resource use and sources for unit costs in the CESAR trial

Resource items	Source	References to sources
<b>From trial entry to discharge from hospital</b>		
Days of organ support	ICU costing study	Hibbert <i>et al.</i> 2005 <sup>51</sup>
Days on ECMO	ICU costing study	Hibbert <i>et al.</i> 2005 <sup>51</sup>
Days on conventional ventilation	ICU costing study	Hibbert <i>et al.</i> 2005 <sup>51</sup>
Days in intensive care	ICU costing study	Hibbert <i>et al.</i> 2005 <sup>51</sup>
Days of other hospital stay before discharge	PSSRU ( <a href="http://www.pssru.ac.uk/uc/uc2005contents.htm">www.pssru.ac.uk/uc/uc2005contents.htm</a> )	Curtis and Netten 2005 <sup>52</sup>
Miles transported by air ambulance	Cost provided by transport provider	
Miles transported by land ambulance	Cost provided by ambulance trusts	
<b>From discharge to follow-up at 6 months</b>		
Telephone contacts with GP	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Contacts with NHS Direct	NHS Direct (2005 personal communication)	
Visits to GP	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Home visits by nurse	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits to counsellor	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits to physiotherapist	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits to occupational therapist	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits by health visitor	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Days of inpatient stay	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Outpatient visits	PSSRU	Curtis and Netten 2005 <sup>52</sup>
A&E visits	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits to day hospital/day care	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Days in residential care	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Days in nursing home	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Medication	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits by social worker	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Visits by home care worker	PSSRU	Curtis and Netten 2005 <sup>52</sup>
Aids and adaptations	Reported by participants and some estimated from personal enquiries by researcher to equipment suppliers	
Value of hours of informal care	Office of National Statistics	Office of National Statistics 2003 <sup>53</sup>
Miles of private car use for health care	Automobile Association	Automobile Association 2007 <sup>54</sup>
Out of pocket expenses	Reported by CESAR trial patients	
Major changes in household	Reported by CESAR trial patients	
Child-care costs	Reported by CESAR trial patients	
Change in employment	Reported by CESAR trial patients	
Change in benefits or allowances	Reported by CESAR trial patients	
Loss of income from employment	Reported by CESAR trial patients	
Other costs	Reported by CESAR trial patients	
Other changes	Reported by CESAR trial patients	
A&E, accident and emergency department; PSSRU, Personal Social Services Research Unit.		

- of resources used during the intensive care ECMO/conventional treatment period.
- (b) Transport form (a) at trial entry – completed by Glenfield Hospital transport team to record transfer of trial participants to ECMO centre or conventional treatment centres.
  - (c) Transport form (b) – completed by Glenfield transport team to record ambulance journey of participants returning either to the original recruiting hospital or another ICU after ECMO.
  - (d) Outcomes data sheet – completed by medical staff, and records date on death of patient (if applicable), date of discharge, date of transfer to another hospital/home, use of ambulance for transfer, etc.
  - (e) Events diary – to be completed and kept by all participants to document all services used from discharge to follow-up as an aide memoire to help them to answer questions at 6 months. This included information about informal help received as well as formal services.
  - (f) Patient cost questionnaire at 6-month follow-up – administered by trained interviewer at patient's home or by telephone to collect resource use data from discharge to follow-up, covering items recorded in (e) above.
  - (g) GP proforma – completed by GPs to collect medication use of those patients who refused the 6-month follow-up but gave permission for use of GP records.

Items (a)–(g) above are reproduced in Appendix 2.

The events diary (e) and the patient cost questionnaire (f) were piloted with five patients discharged from Glenfield Hospital ICU, and the GP proforma (g) was piloted with five general practitioners. Interviewers were trained in the administration of the patient cost questionnaire (f). As it was anticipated that many ambulance trusts across the UK might become involved in transporting trial patients, all ambulance trusts were contacted and agreement obtained to provide costs of patient journeys (including overhead and running costs) as and when they took place during the trial.

Two items of resource use not collected alongside the trial were resource use associated with and following a patient's death in the critical care unit, and costs incurred by relatives whilst visiting patients in intensive care or during a hospital stay. These items were excluded from the data collection from CESAR trial patients because of the practical difficulty of collecting data and because a

well-defined methodology was not available at the early stages of planning the CESAR trial. However, the cost of visiting patients in intensive care was thought likely to be an important social cost, and is being estimated by a separate study in a sample of CESAR centres and is described in more detail below (see Estimating unit costs).

### Resource data collection for the economic evaluation

Following recruitment, the progress of all participants was tracked initially until their discharge from hospital so that resource use could be accurately measured and collected at each stage. During the intensive treatment period (ECMO or conventional ventilation) data were collected on the number of days spent in each treatment mode, including daily information on the number of organs supported and the level of critical care (ICU or high dependency unit). After transfer to another hospital or another ward within the same hospital following the acute phase of the illness, resource use was measured as number of inpatient days up to discharge.

Details of all ambulance use related to transferring trial patients at recruitment were collected by the Glenfield transport team, and details of all other ambulance journeys (for example transfer between hospitals) were collected by the relevant hospitals and sent to the research team. Data collected included date, time, origin and destination of journey, mode of transport (road ambulance, fixed wing aircraft or helicopter), duration of journey, and distance travelled by the patient.

After discharge from hospital, each participant was sent details of the forthcoming interview and the 'events diary' to record resource use. The patient was asked to give permission for one of a series of options to take place 6 months after trial entry: (1) face-to-face interview, (2) telephone interview, (3) postal questionnaire and (4) collection of resource use from GP records. Those patients who were still in hospital at 6 months, if fit enough, were asked to give permission to be interviewed at their hospital bedside using a very short resource use questionnaire.

### Estimating unit costs

In order to estimate the total cost of treatment for each trial participant, the respective quantities of resource use were multiplied by their corresponding unit costs. Some resources used by participants are in the form of actual costs

(not charges) and do not need any valuation. For example, costs of ambulance journeys were obtained directly from the relevant ambulance service providers and incorporated all overhead and running costs. The unit costs of most items of resource use were obtained from nationally available sources.<sup>51,55</sup> Use of medication was valued using the price of drugs listed in the *British National Formulary*.<sup>56</sup> Informal care was valued by the opportunity cost method suggested by Posnett and Jan.<sup>57</sup> Average cost per day of critical care and ECMO was obtained from a separate study and weighted/adjusted for each centre in the CESAR trial (see Cost per day of ICU including ECMO unit care). Cost of visiting was also derived from a separate study (see Costs of visiting patients in intensive care).

Costs of private travel were estimated using Automobile Association (AA)<sup>55</sup> motoring costs, which publishes the average cost per mile for petrol cars annually.

#### **Valuation of informal care time**

In the CESAR trial, informal care time was valued using Posnett and Jan's<sup>57</sup> scenarios: working time where output is replaced; working time where output is not replaced; non-work time of those in paid employment and those not in paid employment; and, finally, for those not in paid employment where unpaid housework is not replaced. Average wage rates for men and women in the UK needed for estimating time costs were obtained from the Office of National Statistics.<sup>53</sup>

#### **Predicted future costs of lifetime care**

It was assumed that for survivors at 6 months, costs of care would remain the same as they were at 6 months' follow-up until 24 months post randomisation. At 24 months, the average health service expenditure for the surviving patients in the CESAR trial was assumed to be the same as that of similar age groups in the UK. The age groups used in predicting future costs and benefits were 16–44 years and 45–64 years. Data on health services' costs for these age groups have been published in the proceedings of Parliament.<sup>58</sup> The same age groups were used as the basis for estimating patients' long-term costs and their benefits.

#### **Price year, inflation, currency and discounting**

Resources and costs were measured in the year in which they occurred using appropriate unit costs for each year of resource use. All costs were then revalued for analysis and reporting to 2005 UK values using health-care inflation estimates.

The duration of follow-up for the short-term analyses was 6 months and therefore discounting was not necessary. For capital costing, annualised values were used based on previous experience with earlier pilot studies relating to the Critical Care National Cost Block study.<sup>59</sup> All costs were based on the 2005 price year. For the lifetime estimates, costs and QALYs were discounted at 3.5%, based on UK treasury guidelines.<sup>60</sup>

#### **Cost per day of ICU including ECMO unit care**

This was a prospective, observational, longitudinal multicentre study (the Critical Care ICU HRG study), concurrent with the CESAR trial, involving a volunteer sample of 70 critical care units, in which monthly data on critical care unit expenditure together with daily data on patients' organ support were collected for a 3-month period.<sup>51</sup> The sample had good geographical coverage in England, with smaller numbers from Scotland and Northern Ireland but none from Wales. An average daily cost of an ICU was estimated by collecting data on the annual expenditure of ICUs and apportioning this sum by their annual throughput of patients.

#### **Data collection**

The critical care units and hospital finance departments were sent questionnaires to document their monthly expenditure on consumables (drugs and fluids, disposable equipment, nutritional products and blood and blood products), staff (consultant medical staff and other medical staff), clinical support services (radiology tests and laboratory services), their use of professionals allied to medicine (physiotherapists, clinical pharmacists, dieticians, medical technical officers, information technologists, clinical and biomedical scientists, speech and language therapists, clinical psychologists and occupational therapists), support staff (personnel officers and directorate accountants) and specialised bed therapy. Data were also collected on the monthly number of patient days, number of staffed beds, number of patient admissions, etc. An average daily cost was calculated using the following formula:

$$\frac{\sum (\text{Monthly expenditure on staff + consumables} + \text{clinical support services})}{\text{Monthly number of total patient days}}$$

Internal validation of the cost data collected was not performed; however, external validation of the estimates was possible using data from the Critical Care National Cost Block Programme.<sup>59</sup> Twenty-

one units in this study (30%) contributed data to the Cost Block Programme for the financial year 2000–1. Although the Cost Block Programme collected data for a different time period and using a different configuration of units, the similarity between the mean costs per patient day is striking, in particular the costs of consumables and clinical support services. The study by Hibbert *et al.*<sup>51</sup> had wider coverage of resources with respect to professionals allied to medicine and an inbuilt allowance for capital equipment, which may be responsible for a slightly higher mean costs per day (£1302, 2003 price year) than for the Cost Block Programme (£1028, 2001 price year; £1119 inflated to 2003 price year).

The completeness of the returned data was investigated by each resource item and expressed as a percentage of the number of responses divided by the total number of 18 possible responses. Data on nursing and administrative staff together with drugs and fluids yielded the highest number of responses (77%). Data on clinical and biomedical scientists and clinical psychologists yielded the lowest number of responses at 14%.

The average daily cost in critical care has to be adjusted to reflect the severity of illness or degree of organ support required by patients. For this purpose data provided by 46 critical care units in the Critical Care ICU Healthcare Resource Group (HRG) study<sup>51</sup> were used. Only those critical care units that supplied data on their expenditure, organ support and unit characteristics were included. The aim was to develop an appropriate model from which estimates of daily case-mix adjusted costs could be determined. Different ways of modelling the organ support and expenditure data were explored. The model of choice was informed by the Breusch-Pagan and Hausman specification tests<sup>61</sup> that favoured a random effects model based on the number of organs supported on a daily basis, clustered to include zero or one organs, two organs, and three or more organs. This model offered a simple and reproducible system of estimating case-mix adjusted costs of care. Daily organ support weights were 0.577 for zero or one organs supported, 1.137 for two organs supported and 1.156 for three or more organs supported.<sup>62</sup> These weights were applied to average daily costs of patients participating in the CESAR trial. A total cost per patient of his or her ICU stay was calculated by weighting patients' average daily cost according to the number of organs supported on a daily basis and summing these daily costs for each patient.

Not all CESAR centres took part in the Critical Care HRG costing study. Separate visits or contacts by correspondence were made with all CESAR centres that did not participate in the Critical Care HRG costing study, including the ECMO centre, to collect the same data to estimate the daily cost in the same way. The response rate of the control centres was low with only 16% of questionnaires returned. In order to estimate average daily costs for each CESAR hospital for the financial year in which a patient(s) was treated, missing data were substituted with mean estimates obtained from the responding hospitals by financial year. A more thorough description of this part of the research is included in Clare Hibbert's PhD Thesis.<sup>63</sup>

### Costs of visiting patients in intensive care

A pilot study of the costs of visiting<sup>64</sup> was carried out in December 2001 at an ICU in the UK. The pilot study informed the methods for a multicentre study in six ICUs in the UK that were registered with the CESAR trial. The aim was to estimate the average cost of visiting patients in intensive care. All adults including primary carers visiting the ICUs during a 3-week period were requested to complete a questionnaire that asked them about their time spent in visiting and travel, out of pocket expenses, employment status, loss of income, etc. Data from this study were used to estimate the average cost of visiting per day.

## Analysis and reporting of costs and economic evaluation

### Estimation of costs for each patient

Costs falling upon the health sector (health and social services), costing falling upon patients/families and other costs, such as help from friends, were presented in total and disaggregated. Resource use and unit costs described above were used to estimate mean, medians, SDs and ranges of costs for each patient in the CESAR trial.

### Cost-effectiveness analysis

With the availability of patient level data on costs and effects, it is possible to summarise uncertainty in the incremental cost-effectiveness ratio as a confidence interval (CI). The focus here is to estimate the CIs for incremental cost-effectiveness

**TABLE 2** Items to test during sensitivity analysis

Item	Ranges and thresholds
Days on ECMO	Highest and lowest observations
Length of stay in critical care unit (ICU and high dependency unit)	Highest and lowest calculated costs
Total length of stay in hospital	Highest and lowest calculated costs
Cost per day on organ support	Highest and lowest calculated costs
Distance from ECMO centre (cost of transport)	Replacing air with road transport
Change in difference in survival	Upper and lower CI of the attributable benefit
Other items with significant cost difference	Highest and lowest observations

ratios when uncertainty is limited to the north-east quadrant of the cost-effectiveness plane (i.e. when the new treatment under evaluation is significantly more costly and more effective). Non-parametric bootstrapping was used to generate CIs.

### Cost-utility analysis

Lifetime incremental cost-utility ratios were estimated using Monte Carlo simulation methods in a simple decision-analytic model,<sup>65,66</sup> and using data and simplifying assumptions described above.

### Sensitivity analysis and uncertainty

Sensitivity analysis based on testing specific assumptions and probabilistic analysis were used to explore the uncertainty in the results.<sup>67,68</sup> Some of

the items tested in the sensitivity analysis are listed in *Table 2*.

Primary analysis was on a complete case basis, whereby a complete case was defined as those meeting the CESAR trial clinical effectiveness data analysis. Any missing values were replaced with imputed values and reanalysed as part of the sensitivity analysis. Missing EQ-5D responses were imputed for the 6-month cost-utility analysis. In the best case all missing values were given perfect health (11111) and in the worst case all missing values given zero health (33333). However, this did not affect the results in any way. Missing EQ-5D responses were not imputed for the lifetime model.

Missing data were imputed using Rubin's multiple imputation method<sup>69</sup> with SOLAS v3.20 (Statistical Solutions Inc., County Cork, Ireland).

## Chapter 3

### Results

Between July 2001 and August 2006, enquiries were made about 766 potentially eligible patients from 148 centres. 180 of these patients (90 in each arm) were randomised from 68 centres. Three patients in the conventional arm did not give permission to be followed up. These patients were alive and had been discharged from hospital but no reliable information is available regarding their level of disability 6 months after randomisation. Information about the primary outcome is available for 177 (98%) patients (*Figure 1*). *Table 3* shows that the groups were broadly comparable at trial entry in terms of key prognostic factors. Note that all of the 85 patients who entered the ECMO arm for hypoxia fulfilled the ARDS criteria according to the American–European Consensus.<sup>70</sup> In the conventional arm, 87 patients entered the study based on hypoxia; 85 out of 87 fulfilled the ARDS criteria and two the acute lung injury (ALI) criteria.

*Table 4* shows the extent to which patients received their randomly allocated management. No patients allocated to CM received ECMO. However, one CM patient was put on an experimental form of lung support (Novalung®, Talheim, Germany), violating the protocol. Seventy-six per cent of patients allocated to transfer for consideration of ECMO were cannulated. Of those who did not receive ECMO, three died before transfer to Glenfield, two died in transit, 16 improved with conventional care, and one patient required amputation and could therefore not be heparinised. The 17 patients who were transferred to Glenfield hospital by the ECMO transport team were managed by the ECMO team conventionally (i.e. attempting to achieve adequate gas exchange without excessive ventilator settings, predominantly  $\text{FiO}_2 < 0.6$ ,  $\text{PIP} < 30 \text{ cmH}_2\text{O}$ ), using the same protocols as the ECMO patients with the exception that ECMO was not used. *Table 4* includes information on compliance with the low volume ventilation strategy (defined as the number of patients in each arm who received low volume ventilation strategy at any time), and the mean proportion of days in critical care during which the strategy was followed for these patients. Both of these parameters were significantly higher in the ECMO arm than in the conventional arm ( $p < 0.001$ ), indicating that more

lung protective ventilation was used in the ECMO arm. As the proportion of total critical care days was used, this parameter was not affected by the lower number of critical care days in the control group.

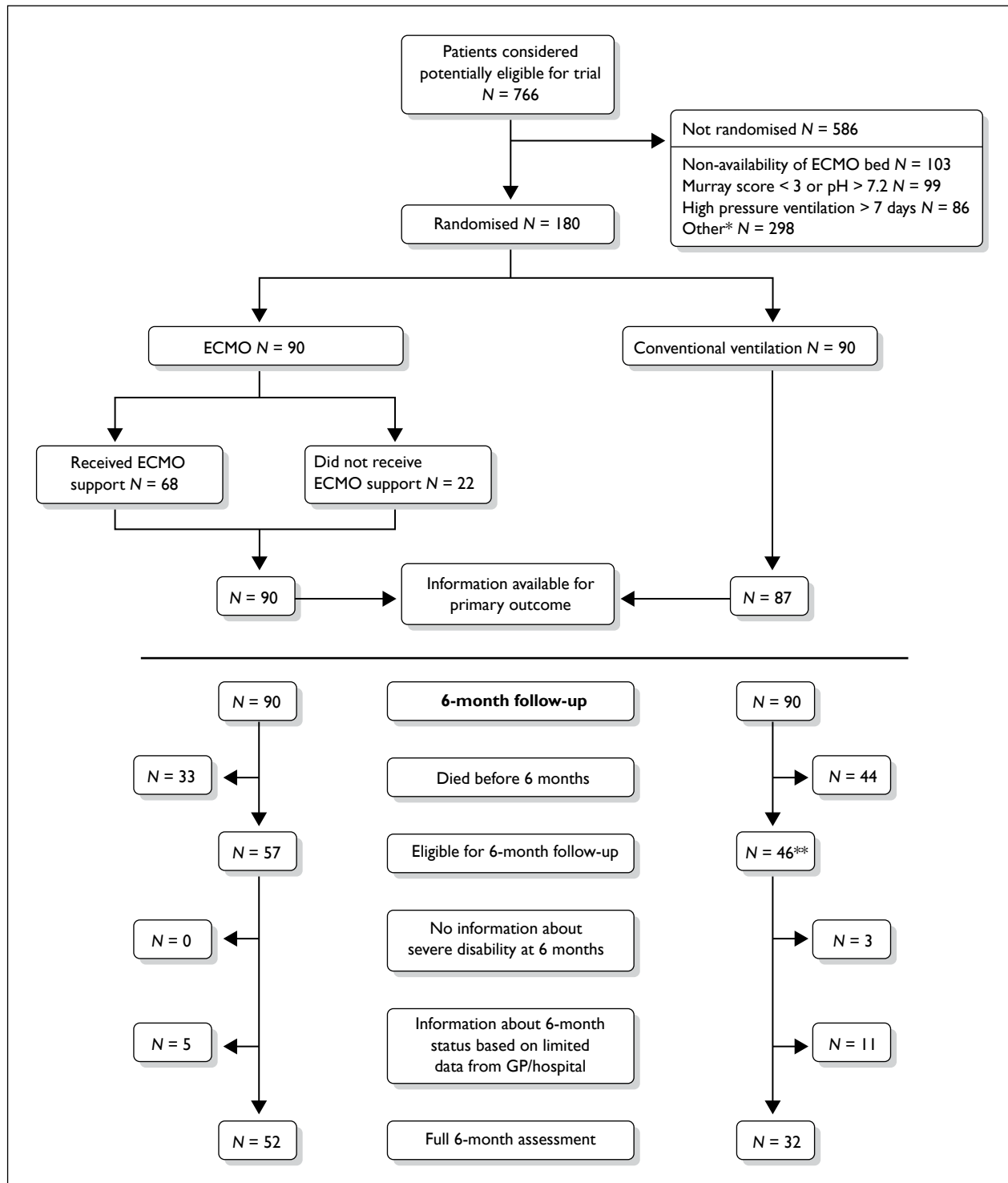
*Table 5* shows that fewer patients in the ECMO arm than in the CM arm had died before 6 months (or later if before discharge home) or were severely disabled 6 months after randomisation, our primary end point [33/90 (36.7%) versus 46/87 (52.9%); RR = 0.69 (95% CI 0.50 to 0.97);  $p = 0.030$ ], i.e. six patients would need to be treated with ECMO to prevent one death or severe disability. Only one patient (in the CM arm) was known to be severely disabled at 6 months. This patient was unconscious and on an oscillator in hospital. Half of the CM patients and 36.7% of the ECMO patients died [RR = 0.73 (95% CI 0.50 to 1.03);  $p = 0.07$ ]. A greater proportion of deaths in the CM arm were classified as due to respiratory failure (*Table 5*).

The time from randomisation to death (*Figure 2*) was considerably shorter in the CM compared with the ECMO arm (log rank test 0.027).

Patients allocated to ECMO spent longer in critical care, and in hospital, than those allocated to CM, especially those who died (*Table 6*).

In the per-protocol analysis, 8 of the 22 patients allocated to ECMO but not receiving it died or were severely disabled (36.4%), a similar proportion to the 68 patients who did receive ECMO. *Tables 7* and *8* describe these two groups and the CM groups in terms of the APACHE II (Acute Physiology and Chronic Health Evaluation II) score and the Murray score and its components at trial entry.

The mean APACHE II score at trial entry was 20, unfortunately 33 patients in the ECMO arm and 29 patients in the conventional arm did not have an APACHE II form completed. The mean  $\text{PaO}_2/\text{FiO}_2$  ratio was 83.2 mmHg in the patients treated without ECMO versus 73.9 mmHg in those treated with ECMO ( $p = 0.24$ ). This mean value does not give a true reflection of this patient group, some of



**FIGURE 1** \*81 were contraindicated to continue with treatment, 35 were only enquiries, 35 received advice on optimal conventional treatment, 33 refused assent, 31 had contraindications to limited heparinisation, 30 were aged < 18 or > 65 years; in 28 cases the clinician refused, eight had an improving condition, for seven the relatives were not available to provide assent, four died prior to randomisation, three had intracranial bleeding, two were given advice on ECMO treatment and one was ineligible due to earlier surgical treatment. \*\*Includes one patient with follow-up assessment at 6 months in hospital and who died after 6 months without leaving hospital.

**TABLE 3** Information at baseline

	Random allocation	
	ECMO (N=90)	CM (N=90)
<b>Hospital of trial entry<sup>a</sup></b>		
CTC	73	75
RH	17	15
<b>Gender</b>		
Male	51	53
<b>Age (years)<sup>a</sup></b>		
18–30	25	23
31–45	29	32
46–65	36	35
Mean (SD)	39.9 (13.4)	40.4 (13.4)
<b>Primary diagnosis at entry<sup>a</sup></b>		
Pneumonia	56	53
Obstetric ARDS	0	0
Other ARDS	25	26
Trauma including surgery within 24 hours	5	7
Other	4 <sup>b</sup>	4 <sup>c</sup>
<b>Number of organs failed<sup>a</sup></b>		
1–2	62	63
≥3	28	27
<b>Duration of IPPV at entry (hours)</b>		
0–48	46	51
49–168	36	32
> 168	6	7
Median (IQR)	35.0 (17.3 to 104.5)	37.0 (15.5 to 101.5)
Missing	2	0
<b>Duration of high-pressure ventilation and/or high FiO<sub>2</sub> at entry (days)<sup>a</sup></b>		
0–48	56	59
49–168	34	31
Median (IQR)	28.5 (17.0 to 69.3)	28.0 (12.0 to 88.0)
<b>Entry based on</b>		
a) Hypoxia <sup>a</sup>	85	87
If yes, Murray score mean (SD)	3.5 (0.6)	(0.3)
<i>Components of Murray score</i>		
PaO <sub>2</sub> /FiO <sub>2</sub> mean (SD)	75.9 (29.5)	75.0 (35.7)
PaO <sub>2</sub> /FiO <sub>2</sub> median (IQR)	73 (57.5 to 87.0)	70.5 (60 to 88)
PEEP mean (SD)	13.7 (9.6)	14.2 (9.4)
Lung compliance mean (SD)	27.4 (12.2)	25.3 (8.0)
Chest radiograph mean (SD)	3.5 (0.7)	3.7 (0.6)
b) Uncompensated hypercapnoea <sup>a</sup>	5	3
If yes, pH mean (SD)	7.1 (0.1)	7.1 (0.1)
<p>a Minimisation criteria.</p> <p>b Asthma; Weil's disease; dermatomyositis; pancreatitis.</p> <p>c Asthma; aspiration; asthma/bronchospasm; acute miliary tuberculosis.</p>		

TABLE 4 Actual management after randomisation

Actual management	Random allocation	
	ECMO (N=90)	CM (N=90)
<b>ECMO received</b>	68 <sup>a</sup>	0
<i>Type of transport to ECMO centre</i>		
Air ( $\pm$ ground)	24	
Ground	38	
Not transferred	6 <sup>b</sup>	
Time between randomisation and starting (hours) – median (IQR)	6.1 (4.0 to 7.1) <sup>c</sup>	
Duration of ECMO (days) – median (IQR)	9.0 (6.0 to 16.0) <sup>d</sup>	
<b>Conventional management (IPPV)</b>		
Transferred for conventional management after randomisation	22 <sup>a</sup>	11
<i>Type of transport to conventional centre</i>		
Air ( $\pm$ ground)	5	2
Ground	14	9
Not transferred	3	79
Duration of IPPV after randomisation (days) – median (IQR)	10 (4.8 to 22.8)	11 (4.0 to 20.3)
<b>Other managements after randomisation</b>		
Missing all data	2	
High frequency/oscillation or jet ventilation	6	13
Nitric oxide	9	6
Prone position	32	38
Steroids	76	58
MARS	15	
Continuous venovenous haemofiltration	72	76
Low volume ventilation strategy at any time	84	63
Proportion of days under low volume ventilation strategy <sup>e</sup> – mean (SD)	0.86 (0.17)	0.67 (0.32)

a Of those who did not receive ECMO, 16 improved with conventional care, three died before transfer to Glenfield, two died in transit and one patient required amputation and could therefore not be heparinised.

b Already in the ECMO centre receiving conventional treatment.

c N=66. Includes one patient whose condition improved on arrival at the ECMO centre so was managed conventionally but then 10 days later deteriorated and ECMO was started.

d N=67. Includes three patients who had a second course of ECMO.

e Based on those under low volume ventilation strategy at all.

whom were so sick that they died before or during transfer and the remainder were not considered sick enough to warrant ECMO by the ECMO team.

In further stratified analyses as specified in the protocol, no significant interactions between the minimisation criteria and the treatment group with respect to the primary outcome were found (Table 9).

Table 10 provides further information about the 6-month follow-up assessment. The first two EQ-

5D questions (mobility and self-care) were used to define severe disability in our primary outcome, and answered by proxy for five patients in ECMO and seven in CM, hence missing values are less than the other components of EQ-5D and other elements of the follow-up assessment. None of the differences between groups were statistically significant at the 5% level.

The time from randomisation to death (Figure 2) was considerably shorter in the CM than in the ECMO arm (log rank test 0.027).

TABLE 5 Primary outcome

	Allocation		
	ECMO (N=90)	CM (N=90)	RR (95% CI)
<b>Death or severe disability at 6 months</b>			
No	57	41	0.69 (0.05 to 0.97) ( <i>p</i> =0.03) <sup>a</sup>
Yes	33	46	
No information about severe disability at 6 months	0	3	
<b>Died ≤ 6 months or died before discharge</b>			
No	57	45	0.73 (0.52 to 1.03) ( <i>p</i> =0.07)
Yes	33	45	
<b>Severe disability</b>			
Yes	0	1	
No	57	41	
Died ≤ 6 months before discharge	33	45	
No information about severe disability at 6 months	0	3	
<b>Cause of death</b>			
Respiratory failure	8	24	
Multi-organ failure	14	15	
Neurological	4	2	
Cardiovascular	1	3	
ECMO related	1	0	
Other	1	0	
Unknown	4	1	
<b>Randomisation to death interval (days)</b>			
Median (IQR)	15 (3.0 to 40.5)	5 (2 to 14)	
<p>a Based on 187 patients with known primary outcome. The three patients in the CM group for whom the severe disability status at 6 months was unknown had all been discharged from hospital 1–3 months post randomisation and were known to be alive at 6 months. Sensitivity analyses assuming that these three patients had all been or not been severely disabled change these figures to RR=0.67 (95% CI 0.48 to 0.94), <i>p</i>=0.017, and RR=0.72 (95% CI 0.51 to 1.01), <i>p</i>=0.051 respectively.</p>			

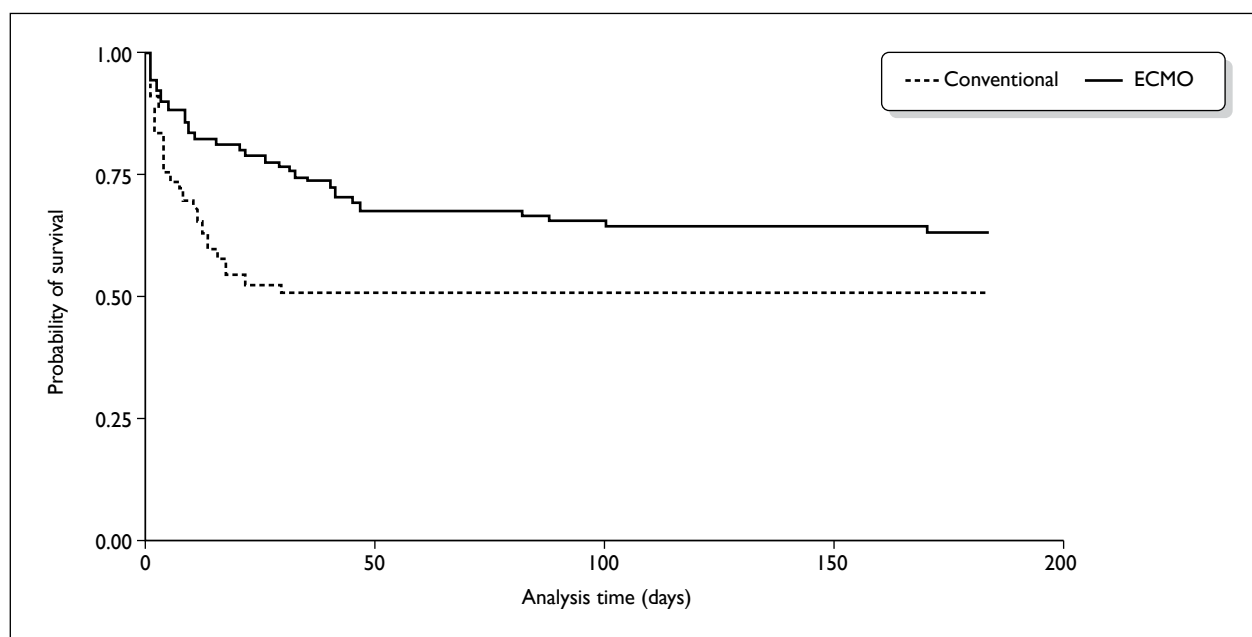
## Economics results

Resource use data were collected for all patients included in the CESAR trial, so costs could be estimated for all participants. Although final primary outcome data for clinical effectiveness were available from all but three patients, complete EQ-5D data were missing in 17 cases.

Table 11 shows that patients allocated to ECMO were transported further for care and so used more transport. There was also a trend for them to have more organ systems supported and to stay longer in hospital than those allocated to CM. Surviving

patients allocated to ECMO and returning home required more nursing and other therapy and social services, per patient, than those receiving CM, but the mean differences were not statistically significant. All other health-care use was similar between groups.

Table 12 shows that the majority of costs incurred were for health care, and the highest care costs resulted from the initial hospitalisation. Both groups of patients surviving to hospital discharge had considerable time given by family and friends, amounting to a value of £4332 per patient in the ECMO group, and £2212 in the CM group. This



**FIGURE 2** Kaplan–Meier survival estimates, by allocation.

**TABLE 6** Length of stay

	<b>ECMO (N=90)</b>	<b>CM (N=90)</b>
Days in critical care – median (IQR)	24.0 (13.0 to 40.5) <sup>a</sup>	13 (11 to 16)
Days in hospital – median (IQR)	35.0 (15.6 to 74.0)	17.0 (4.8 to 45.3)
<b>Deaths only</b>	<b>N=33</b>	<b>N=45</b>
Days in critical care – median (IQR)	11 <sup>a</sup> (2 to 28)	5.0 (2.0 to 13.5)
Days in hospital – median (IQR)	15 (3.0 to 40.5)	5.0 (2.0 to 13.5)

a Excludes one patient whose notes are still with the coroner.

**TABLE 7** Primary outcome and APACHE II scores

	<b>ECMO: yes (N=68)</b>	<b>ECMO: no (N=22)</b>	<b>CM (N=90)</b>
<b>Death or severe disability</b>			
Yes	25	8	46
No	43	14	41
Missing			3
<b>APACHE II score</b>			
Mean (SD)	20.5 (7.0)	18.2 (3.5)	19.9 (6.1)
Missing	27	6	29

**TABLE 8** Murray scores and components

	ECMO: yes	ECMO: no	CM
Entry based on hypoxia (n)	65	20	87
Murray score mean (SD)	3.4 (0.3)	3.6 (1.3)	3.4 (0.3)
<i>Components of Murray score</i>			
PaO <sub>2</sub> /FiO <sub>2</sub> mean (SD)	73.8 (29.9)	83.2 (27.7)	75.0 (35.7)
PaO <sub>2</sub> /FiO <sub>2</sub> median (IQR)	70.0 (55.5 to 87)	80 (62 to 105)	70.5 (60 to 88)
PEEP mean (SD)	14.5 (11.0)	11.5 (2.1)	14.2 (9.4)
Lung compliance mean (SD)	27.1 (13.0)	28.4 (9.9)	25.3 (8.0)
Chest radiograph mean (SD)	3.5 (0.7)	3.5 (0.8)	3.7 (0.6)

**TABLE 9** Stratified analyses by minimisation factors

Minimisation factor	Severe disability or death by 6 months			p-value (for interaction test)
	ECMO n/N (%)	CM n/N (%)	RR	
<b>Hospital of trial entry</b>				
CTC	30/73 (41.1)	38/73 (52.1)	0.79 (0.56 to 1.12)	0.12
RH	3/17 (17.7)	8/14 (57.1)	0.31 (0.10 to 0.95)	
<b>Age (years)</b>				
18–30	8/25 (32.0)	12/22 (54.6)	0.59 (0.30 to 1.17)	0.20
31–45	7/29 (24.1)	15/31 (48.4)	0.50 (0.24 to 1.05)	
46–65	18/36 (50.0)	19/34 (55.9)	0.89 (0.57 to 1.39)	
<b>Primary diagnosis at entry</b>				
Pneumonia	21/56 (37.5)	29/51 (56.9)	0.66 (0.44 to 1.00)	
Other ARDS	8/25 (32.0)	14/25 (56.0)	0.57 (0.29 to 1.11)	
Trauma including surgery within 24 hours	2/5 (40.0)	1/7 (14.3)	2.8 (0.34 to 23.06)	
Other	2/4 (50.0)	2/4 (50.0)	1 (0.25 to 4.0)	0.59
<b>Number of organs failed</b>				
1–2	15/62 (24.1)	27/60 (45.0)	0.54 (0.32 to 0.91)	0.10
≥ 3	18/28 (64.3)	19/27 (70.4)	0.91 (0.63 to 1.32)	
<b>Duration of high pressure ventilation and/or high FiO<sub>2</sub> at entry (hours)</b>				
0–48	21/56 (37.5)	28/57 (49.1)	0.76 (0.50 to 1.17)	0.56
49–168	12/34 (35.3)	18/30 (60.0)	0.59 (0.34 to 1.01)	
<b>Mode of trial entry</b>				
Hypoxic	31/85 (36.5)	44/84 (52.4)	0.70 (0.49 to 0.98)	0.83
Hypercarbic	2/5 (40.0)	2/3 (66.7)	0.60 (0.16 to 2.29)	

TABLE 10 Six-month follow-up assessment

	ECMO (N=90)	CM (N=90)
Alive at 6 months or discharged alive	57	46
Full follow-up information available	52	32
Limited information from GP/hospital	5	8
Information on death and disability status only	0	3
Alive but no further information available	0	3
EQ-5D	57	40
<i>Problems with mobility</i>		
No problems in walking about	30	19
Some problems in walking about	26	19
Confined to bed	0	2
Missing	1 <sup>a</sup>	0
<i>Problems with self-care</i>		
No problems with self-care	42	26
Some problems washing or dressing myself	13	11
Unable to wash or dress myself	2	2
Missing	1 <sup>a</sup>	1 <sup>b</sup>
Follow-up information available	52	33
<i>Usual activities</i>		
No problems with performing usual activities	21	10
Some problems with performing usual activities	25	19
Unable to perform usual activities	6	4
<i>Pain/discomfort</i>		
No pain or discomfort	23	13
Moderate pain or discomfort	22	18
Extreme pain or discomfort	7	2
<i>Anxiety/depression</i>		
Not anxious or depressed	23	21
Moderately anxious or depressed	26	9
Extremely anxious or depressed	3	3
Overall health status (visual analogue scale)(higher score indicates better health)		
Mean (SE)	67.9 (2.8)	65.9 (3.8)
Missing	0	1
<i>Compared with a year ago</i>		
Better now	9	2
Somewhat better now	5	2
About the same	9	5
Somewhat worse now	18	13
Much worse now	11	9
Missing	0	1
SF-36 – mean (SE) (higher = better)		
Physical functioning	64.5 (4.2)	60.0 (5.9)
Missing	2 <sup>a</sup>	1
Role: physical	58.2 (4.8)	46.3 (6.5)
Bodily pain	66.2 (4.2)	62.2 (5.0)

**TABLE 10** Six-month follow-up assessment (continued)

	ECMO (N=90)	CM (N=90)
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)
Role: emotional	72.6 (4.3)	71.4 (5.6)
Mental health	70.5 (3.0)	65.5 (3.7)
St George's Hospital Respiratory Questionnaire – mean (SE) (higher = worse)		
Symptom score	32.4 (3.3)	41.2 (4.5)
Missing	0	1
Activity score	29.5 (3.7)	38.4 (5.4)
Missing	2 <sup>a</sup>	
Impacts score	15.0 (2.4)	18.8 (3.1)
Total score	22.4 (2.7)	27.6 (3.6)
Missing	2 <sup>a</sup>	1
Mini-Mental State Examination – mean (SE) (lower value = more problems with cognition)		
Below normal (<24)	2	2
Missing	3 <sup>b</sup>	1
HADS depression score – mean (SE) (higher value = more depression)		
Significant depression (score 11–21)	4	4
Missing	2	0
HADS anxiety score – mean (SE) (higher value = more anxiety)		
Significant anxiety (score 11–21)	7	10
Missing	2	0
Sleep problems score – mean (SE) (higher = more problems)	16.7 (3.2)	18.8 (3.6)
Caregiver strain index		
Low	8	2
High (score 7 or more)	9	6
Missing	2 <sup>b</sup>	0
Not applicable (no carer)	33	24
Restrictions to upper limb movement	3	5
Missing	2 <sup>b</sup>	1
Lung capacity – mean (SE)		
FEV <sub>1</sub> (litres)	2.6 (0.1)	2.5 (0.1)
FEV <sub>1</sub> % of predicted	74.9 (2.0)	72.9 (3.3)
FVC (litres)	3.3 (0.1)	3.2 (0.2)
FVC % of predicted	79.6 (2.4)	79.9 (3.6)
FER (%)	81.9 (1.5)	81.6 (2.2)
FER % of predicted	101.0 (1.7)	100.7 (2.5)
PEFR (litres/minute)	370.7 (16.1)	364.3 (20.5)
PEFR % of predicted	74.5 (2.4)	75.1 (3.6)
Missing	3	2

FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; FER, forced expiratory ratio; HADS, Hospital Anxiety and Depression Scale; PEFR, peak expiratory flow rate.

a One patient in a wheelchair and did not answer mobility question, and one patient had limited mobility so left out those sections.

b Severe alcohol-related problems so very limited follow-up available.

TABLE 11 Use of health-care services by patients in the CESAR trial

	ECMO (N=90)		CM (N=87)		Difference, mean (95% CI)
	Total	Mean	Total	Mean	
<b>Resource use from trial entry to discharge from hospital</b>					
Air ambulance (miles)	5538.98	61.54	605.50	6.96	54.58 (26.74 to 82.43)
Road ambulance (miles)	22,797.96	253.31	6412.81	73.71	179.60 (121.92 to 237.28)
0–1 organs supported (number of days)	1380	15.33	1095	12.59	2.75 (–2.35 to 7.84)
2 organs supported (number of days)	627	6.97	478	5.49	1.47 (–1.28 to 4.23)
≥3 organs supported (number of days)	750	8.33	426	4.9	3.44 (–0.44 to 7.32)
Other hospital stay (number of days)	1607	17.86	1329	15.28	2.58 (–5.25 to 10.41)
<b>Resource use from discharge to follow-up at 6 months</b>					
Travel home after discharge (miles)	914.40	10.16	70	0.80	9.36 (0.45 to 18.26)
GP surgery services (times)	173	1.92	188	2.16	–0.24 (–1.21 to 0.73)
Telephone calls to NHS professionals (times)	19	0.21	50	0.57	–0.36 (–1.11 to 0.39)
Visits to nurse (times)	357	3.97	309	3.55	0.41 (–4.53 to 5.36)
Visits to physiotherapist (times)	240	2.67	246	2.83	–0.16 (–3.83 to 3.51)
Visits to occupational therapist (times)	65	0.72	14	0.16	0.56 (–0.17 to 1.30)
Counselling (times)	11	0.12	21	0.24	–0.12 (–0.55 to 0.31)
Other nursing, therapy and social services (times)	425	4.72	21	0.24	4.48 (–3.59 to 12.55)
Inpatient stay (days)	122	1.36	63	0.72	0.63 (–1.03 to 2.29)
Outpatient visits (times)	121	1.34	104	1.21	0.14 (–0.50 to 0.77)
Other hospital services (times)	12	0.13	84	0.97	–0.83 (–3.13 to 1.46)
Nursing home and residential care (days)	3.43	0.04	9	0.10	–0.07 (–0.28 to 0.15)
Help/support from family/friends (hours)	29,198.5	324.43	14,388	165.38	159.05 (–12.99 to 331.08)

excludes the costs of visiting during the initial hospital stay (see below for results of the survey of costs of visiting)

Mean health-care costs per patient were more than twice as high for the patients allocated to ECMO (£73,979) than for those allocated to CM (£33,435), a difference of £40,544 (95% CI £24,799 to £56,288). As is usual, health-care costs were quite skewed and highly variable between patients.

Based on a simple budget impact analysis, and using the same costing assumptions listed above, we have estimated that the additional cost to the health service of a policy of providing access to the ECMO service would be £4,828,320 per year for 120 patients and £14,082,600 per year for 350 patients.

## Cost-effectiveness analysis

The base-case analysis (from the NHS viewpoint and so excluding patients' costs) found the incremental cost-effectiveness of ECMO to be £250,162 per additional survivor without severe disability. *Table 13* also presents the results of the sensitivity analysis for alternative methods for cost estimation.

## Cost-utility analysis

*Table 14* reports the incremental cost-utility ratios for different scenarios from the NHS viewpoint, illustrating the results of the cost-utility analysis according to changes in the key assumptions. The mean gain in QALYs at 6 months post

**TABLE 12** Costs per CESAR trial participant (2005 prices)

	ECMO (N=90), mean (£)	CM (N=87), mean (£)	Cost difference, mean (95% CI) (£)
<b>Recruitment to discharge</b>			
Air ambulance	2175	425	1750 (891 to 2609)
Land ambulance plus staff	815	205	609 (484 to 734)
Cost of 0–1 organs supported	20,542	10,260	10,281 (4730 to 15,834)
Cost of 2 organs supported	19,590	8939	10,652 (4428 to 16876)
Cost of ≥ 3 organs supported	24,928	7986	16943 (7742 to 26,143)
Cost of other hospital stay	5531	4732	799 (–1672 to 3270)
<b>Discharge to 6 months</b>			
Travel home after discharge	18	1	16 (0.44 to 32)
GP surgery services	59	64	–5 (–36 to 26)
Phone calls to NHS professionals	4	11	–7 (–20 to 7)
Visits to nurse	85	73	12 (–67 to 92)
Visits to physiotherapist	118	124	–6 (–138 to 126)
Visits to occupational therapist	25	6	19 (–0.41 to 39)
Counselling services	8	5	4 (–8 to 15)
Other nursing, therapy and social services	78	10	68 (–37 to 173)
Inpatient stay	420	224	196 (–328 to 719)
Outpatient visits	125	113	13 (–47 to 72)
Other hospital services	9	93	–84 (–198 to 31)
Nursing home and residential care	20	39	–19 (–104 to 67)
Medication	119	88	31 (–106 to 168)
Aids and adaptations	19	6	12 (–8 to 33)
Hospital transport – discharge to follow-up	5.39	5.65	–0.3 (–10 to 9)
Unpaid help from family/friends	4332	2212	2119 (–139 to 4377)

randomisation for those patients allocated to ECMO was 0.03 (95% CI 0.00 to 0.06) and the cost per additional QALY at 6 months post randomisation was £1,631,124.

Individual patient costs were estimated using 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 13* and *14*, and in both cases reduce costs per outcome gained from the ECMO treatment option.

The predicted lifetime incremental cost per QALY discounted at 3.5% (scenario 3 in *Table 14*) was £19,252 (95% CI £7622 to £59,100). If discount

rates were assumed to be zero (that is, future values are worth the same as current values), total costs and total QALY gain were both higher, and the cost–utility of ECMO improves (scenario 4 in *Table 14*).

There is considerable uncertainty in these estimates, as the confidence limits in *Table 14* show.

*Figure 3* illustrates the cost-effectiveness acceptability curve for lifetime estimates,<sup>68</sup> showing the probability (vertical axis) that a policy of ECMO would be cost-effective at different thresholds of willingness to pay at 2005 prices (horizontal axis). This shows that ECMO has a more than 50% chance of being cost-effective at any threshold of spending over around £20,000.

**TABLE 13** Cost-effectiveness of allocation to ECMO compared with conventional management

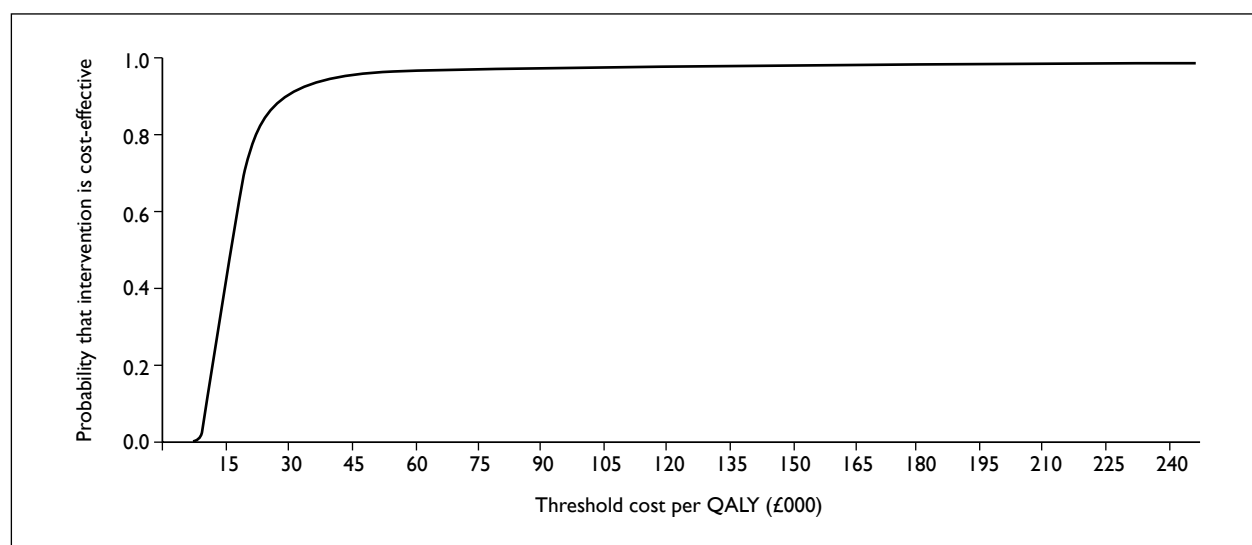
Scenario	ECMO		CM		ICER <sup>b</sup> (£)
	Mean cost (£) (N=90)	Survival (years) <sup>a</sup> (N=90)	Mean cost (£) (N=87)	Survival (years) <sup>a</sup> (N=87)	
1: base case <sup>c</sup>	73,979	0.63	33,435	0.47	250,162
2 <sup>d</sup>	57,534	0.63	36,688	0.47	128,621

a Probability of survival to 6 months.  
b Incremental cost-effectiveness ratio (difference in costs/difference in effects).  
c Total days spent in critical care grouped into three categories based on number of organs supported: 0–1 organs, 2 organs and ≥3 organs, and valued accordingly. Average unit costs applied for all other resource use.  
d Total days spent in critical care grouped into three categories: ECMO days, ICU days and high dependency unit days, and average costs applied. Average unit costs applied for all other resource use.

**TABLE 14** Cost-utility analysis results for CESAR trial (bootstrap estimates)

Scenario	QALYs gained	Additional cost (£)	ICER (95% CI) (£)
1 <sup>a</sup>	0.03	44,191	1,631,124 (–3,242,953 to 11,463,378)
2 <sup>b</sup>	0.03	26,772	732,818 (223,832 to 491,808)
3 <sup>c</sup>	3.66	48,533	19,252 (7622 to 59,100)
4 <sup>d</sup>	7.01	53,896	9389 (4580 to 31,877)

a Outcome – QALYs gained at 6 months, costs based on primary research study (see text).  
b Outcome – QALYs gained at 6 months, costs based on NHS tariffs (see text).  
c Lifetime predicted costs and QALYs, discounted at 3.5%.  
d Lifetime predicted costs and QALYs, undiscounted.

**FIGURE 3** Cost-effectiveness acceptability curve – lifetime estimates discounted at 3.5%.

## Results of costs of visiting study

A total of 334 visitors visited the six ICUs over the 3-week period. Of these, 17 visitors refused to take part in the study, 24 visitors had to be excluded under the exclusion criteria and 77 visitors could not be recruited for other reasons. Information leaflets and questionnaires were given out to the remaining 216 visitors and 173 questionnaires were returned (response rate 80% of eligible visitors).

Table 15 shows the characteristics of respondents. Visitors were mainly close family members and relatives (95%) who came almost daily until the patient's discharge. Some made multiple visits at different times during the same day. Relatives spent several hours by the bedside talking to patients, reading out letters/newspapers, showing photographs, and sometimes alerting the nurse to changes in the patient. Some helped with minor tasks such as wiping the patient's face and adjusting the blanket. Personal care such as body baths, changing bed sheets, etc. was carried out by nursing staff.

**TABLE 15** Visitor characteristics (N = 173)

Gender	
Male	58 (34%)
Female	113 (65%)
Missing data	2 (1%)
Age	
Range	18–85 years
Mean	49.3 years
Median	48 years
Visitors < 65 years	144 (83%)
Visitors ≥ 65 years	26 (15%)
Visitors in paid employment	104 (61%)
Incomplete data	3 (1.7%)
Relationship to patient	
Spouse/partner	47 (28%)
Close relatives (children, parents)	90 (53%)
Other relatives	25 (15%)
Friends/neighbours	9 (5%)
Incomplete data	3 (1.7%)
Percentages are based on total of valid responses to each question.	

## Out of pocket expenses

The out of pocket expenses incurred by visitors were those related to travel, car parking, child care, accommodation and refreshments.

### Travel

Visitors travelled a mean distance of 29.97 miles (one-way) to the ICU; range 0.25–31,000 miles. The distribution was skewed to shorter journeys, indicated by the range and a median value of 10 miles (Table 16).

One hundred and sixteen visitors (67%) travelled by their own car, with a further 39 (23%) sharing a car with a friend/relative. The total number of people who travelled by car was 155 (90%). Fifty-eight (58) visitors (34%) paid parking fees. Thirteen visitors (8%) travelled by taxi, bus or train, three (2%) travelled by plane and two (1%) walked. The distance between home and ICU is heavily skewed because of five visitors who travelled from abroad.

Cost of private car travel was calculated using published AA motoring costs for price year 2005. The estimate used for this study was £0.3578 per mile, which includes standing and running costs for a new petrol car priced between £10,000 and £13,000, with annual mileage 15,000, and the average cost of unleaded petrol for 2005 which was £0.878 per litre.

### Child care, care of dependent relatives and care of pets

Thirty-three visitors (19.1%) had to arrange child care. Of these, two (1.2%) paid for child care, three (1.7%) brought their children with them and 28 (16.2%) made arrangements with relatives. Eight (4.6%) visitors arranged care for other dependent relatives with other relatives or friends. Thirty (17.3%) visitors arranged care for their pets. Of these, 27 (15.6%) made arrangements with relatives and three (1.7%) paid for care.

### Accommodation

Thirty-five visitors (19.4%) needed overnight accommodation. The reasons for this were distance of ICU from home and the severity of the patient's condition. Of these, only nine paid for

accommodation, the remaining 26 answered 'not applicable' to the question regarding payment.

## Refreshments

One hundred people (57.8%) purchased food or drinks. Five visitors (2.9%) did not answer this question.

The mean out of pocket expenses of the 173 study participants are shown in *Tables 17* and *18*.

Visitors were asked about activities forgone (activities they would have been doing) for the visit and leave arrangements for those in employment (*Table 19*). Participants could indicate more than one category, so totals add to more than the total

number of respondents. Of the 173 participants, 104 (60.1%) were in paid employment, one in voluntary work (1%), 41 (23.7%) doing housework, 33 (19.1%) retired and the remaining 12 (6.9%) engaged in other activities. Of those in employment, 24 (23.3%) took annual leave, 28 (27.2%) had obtained compassionate leave, 13 (12.6%) took unpaid absence from work, 32 (31.1%) came outside of their work time and six (5.8%) intended to make the time up. *Table 20* shows the daily time forgone by visitors for the visit and the actual time spent with the patient.

Total time forgone was estimated as the difference between time of leaving home and the time expected to be back home (*Table 20*). Average costs of this time forgone are shown in *Table 21*.

**TABLE 16** Distance travelled by visitors (N = 173)

	Range (miles)	Mean (miles)	Median (miles)	SD (miles)
Distance between home and ICU	0.25–31,000	29.97	10.1	2425.01

**TABLE 17** Out of pocket expenses (N = 173) (pounds sterling at 2005 prices)

	Numbers (%)	Range	Mean	Median	SD	95% CI
Travel: own car (standing and running costs)	116 (67%)	0–214.7	15.0	2.3	31.9	10.2 to 19.8
Travel: bus, taxi, train	13 (8%)	0–600	10	0	56.6	1.5 to 18.5
Parking fees	57 (33%)	0–14	1.2	0	2.2	0.8 to 1.5
Travel: plane	3 (2%)	0–3400	35.3	0	303.5	–10.2 to 80.9
Accommodation	35 (19.4%)	0–179	2.6	0	15.7	0.3 to 5.0
Child care and care of pets	71 (41%)	0–50	0.92	0	5.9	0.05 to 1.8
Food and drinks	100 (57.8%)	0–40	4.5	1	8.0	3.3 to 5.7

**TABLE 18** Average out of pocket and travel costs per participant (N = 173) (pounds sterling at 2005 prices)

	Range	Mean	Median	SD	95% CI
Total out of pocket expenses including air travel	0–3423	69.5	9.2	310.1	22.9 to 116.02
Total out of pocket expenses excluding air travel	0–600	34.2	9.2	69.8	23.7 to 44.6

**TABLE 19** Activities forgone and leave arrangements

	Number	Percentage
<b>Category of activities (N = 173)<sup>a</sup></b>		
Working in paid employment	104	60.1
Voluntary work	1	0.6
Housework	41	23.7
Other	12	6.9
Retired	33	19.1
<b>Leave arrangements (N = 104)</b>		
Took annual leave	24	23.3
Compassionate leave	28	27.2
Unpaid absence	13	12.6
Will make time up	6	5.8
Came outside of work time	32	31.1

a Participants could indicate more than one category, so totals add to more than the total number of respondents.

**TABLE 20** Time forgone (N = 173) (hours)

	Range	Mean	Median	SD
Total time forgone for the visit	0.20–24 <sup>a</sup>	6.6	5.0	5.8
Time spent with patient	0.05–24 <sup>a</sup>	3.9	2.2	5.0

a Maximum time 24 hours because the study looked at *daily time* forgone by visitors. In a day, time cannot be more than 24 hours.

**TABLE 21** Average cost of time forgone and lost pay (N = 173) (pounds sterling at 2005 prices)

Daily costs	Range	Mean	Median	SD	95% CI
Cost of time forgone	1.7–255.8	59.6	40.2	55.5	51.3 to 68.0
Lost income due to unpaid leave	0–206.4	6.9	0	29.2	2.5 to 11.2



# Chapter 4

## Discussion

### Clinical effectiveness

This study showed an important improvement in outcome when a strategy of transferring patients to a specialist centre for consideration of ECMO was used to manage adults with severe but potentially reversible respiratory failure rather than continued conventional ventilation. As hypothesised, transfer for consideration of ECMO reduced the proportion of patients who died or were severely disabled 6 months after randomisation by approximately one-third compared with those in the conventional arm [although the rate in the control arm (52.9%) was lower than expected in the second power calculation (65%)]. The primary outcome measure that the trial was powered to detect was a difference in death or severe disability at 6 months post randomisation. Whilst this is a composite end point, it addresses failings of previous studies by detecting late deaths and also ensures that the survival is meaningful from a societal and individual standpoint. The hospital mortality was also lower in the ECMO arm, although it did not reach statistical significance, but this was not what the study was powered to detect. The APACHE II score is commonly used to estimate disease severity and is a predictor of mortality in patients with ARDS.<sup>71,72</sup> The reported APACHE II score in case series of patients with ARDS varies significantly, ranging between 13.4 and 28.7.<sup>73,74</sup> Whilst the mortality of patients in the conventional arm of CESAR may appear to be high for an APACHE II score of 20, it is comparable with that reported for a similar group of patients (Murray score of 3.4 and PaO<sub>2</sub>/FiO<sub>2</sub> 98 and APACHE II 21.5) in which the mortality was 67%.<sup>19</sup> The time from randomisation to death was significantly shorter in the control arm than in the ECMO arm of the study and a higher proportion of patients in the control arm were listed as dying of respiratory failure, and it is likely that this explains the more rapid onset of death. In the ECMO arm the use of extracorporeal support prevents death from respiratory failure allowing the disease process to either recover or progress to fatal multisystem organ failure. It is possible that clinicians in the control arm withdrew care sooner in patients when they felt that further treatment was futile, whilst the ECMO team had a policy of withdrawing intensive care only in very selected

cases after several weeks of attempted treatment. The data collected do not allow us to determine if there was a systematic bias to explain the difference in time to death between the two groups; however, the investigators believe that the difference is explained adequately by the effect of ECMO in supporting gas exchange and preventing early death from respiratory failure.

The trial design meant that the risk of bias was low as the clinical ECMO team was blinded to the outcome in the control arm; only the staff and members of the DMC knew the outcome in both arms of the study. In addition, minimisation criteria were used in the randomisation to ensure equality between the groups for variables that in previous series of ECMO patients had been shown to have an impact on outcome. This policy was successful in that both groups had equal numbers of very similar patients.

A potential limitation is the pragmatic design with the conventional treatment undertaken in 43 different hospitals. This design was chosen as the only realistic possibility in the UK. Firstly, there was no funding available for treatment of conventional patients in a single centre. Secondly, there was no single unit in the UK that had the infrastructure to accept such an influx of patients allocated to CM, except for Glenfield Hospital. It was not, however, felt appropriate for Glenfield to treat all the patients in both arms. The reasons for this were that the Glenfield team is known to be enthusiastic in the use of ECMO and could therefore be perceived as both less committed to and less skilled in conventional intensive care management. Indeed, a number of intensivists stated that they did not consider the surgical ICU in the Glenfield ECMO unit to be competent to provide conventional intensive care and would not be willing to transfer patients to a study in which all the treatment for both arms was provided at the Glenfield Hospital. Many intensivists from CTCs also stated that they were unwilling to transfer patients out for conventional treatment in another hospital. In addition to these factors, the ECMO team felt that it would be very difficult for clinical staff and relatives to have patients on different treatments in close proximity in a study with no

possibility of cross-over, especially if a patient was doing badly on a particular treatment. The trial team also considered the possibility of protocolising the conventional intensive care received by the control patients. The team approached the Intensive Care Society and also gave numerous presentations at regional intensive care meetings. Unfortunately there was no national consensus and no support for protocolised care. We elected to be pragmatic about the treatment in the control arm, as we knew from the previous pattern of ECMO patient referral that a large number of ICUs would be involved, thereby giving a representative example of 'normal' intensive care treatment in the UK. It can be argued that conventional treatment in a specialist centre could give improved results to those seen in the control arm of the CESAR study; this could perhaps be the focus of a future study.

Although the low volume ventilation strategy from the ARDSNet study was recommended for use by treating intensivists, it was not enforced, so patients in the conventional arm received many different approaches during their treatments. It is important to recognise that the patients in the CESAR trial were much more hypoxic than those in the ARDSNet study,<sup>3</sup>  $\text{PaO}_2/\text{FiO}_2$  ratios of 76.2 and 75.0 mmHg for ECMO and control groups respectively versus 138 and 134 mmHg for treatment and control groups respectively in ARDSNet. It is likely that the low compliance with the low volume strategy is in part because of worse lung disease in the CESAR patients than those in ARDSNet. It is possible that if CM had been rigorously protocolised and provided in a single centre or a small number of centres, the outcome in the control group could have been slightly better. However, this could have led to bias, as the conventional treatment protocol would have been set in 1998–9 and could not have been adapted thereafter, so the protocol would not have included more recent changes in intensive care medicine such as activated protein C,<sup>75</sup> sepsis care bundles<sup>76,77</sup> and conservative strategy of fluid management.<sup>78</sup> So it is also possible that a superseded CM protocol could have reduced survival in the control arm. By allowing intensivists to provide the best treatment that they could, we allowed adaptation of treatment to include recent advances and also examined the actual outcome of intensive care for severe respiratory failure in the UK.

The reality of intensive care admission for the majority of adult patients with respiratory failure in the UK is that they will not be transferred out from their original hospital to a larger unit however bad

their respiratory failure is. Thus the outcome in the control arm should be an accurate reflection of prognosis for patients with severe respiratory failure in the majority of UK ICUs.

By nature of its complexity, ECMO treatment should be provided only in specialist centres. Much as aircraft should be flown only by suitably qualified pilots, the skill set required for safe provision of ECMO needs to be learnt over a number of years in an appropriately skilled ECMO centre. Almost every aspect of the patient and circuit management can result in the instant demise of the patient if not carried out according to established ECMO management protocols. It is beyond the scope of this monograph to include a description of every aspect of ECMO patient management. Although the Glenfield ECMO team is one of the most experienced in the world there was one complication of ECMO cannulation that resulted in the death of the patient. There were no other major complications of ECMO. This concentration of patients with severe respiratory failure within one unit may have led to an expert centre effect in that transferring patients to a surgical ICU that specialises in severe respiratory failure treatment could account for some of the improvement in outcome as the ECMO staff were more used to caring for patients with severe respiratory failure than were the referring units, and possibly were more used to using gentle ventilation with permissive hypoxia and hypercapnia when they knew that ECMO was instantly available should the patient deteriorate. The survival in the treatment arm was the same in the patients who were treated with or without ECMO. This could be because the clinicians correctly identified which patients did not require ECMO and put only the more severely ill on to ECMO (although it is also possible that they were remiss and could have obtained better survival by putting all the patients on ECMO). It is highly unlikely that survival in the ECMO arm would have been so good if all the patients had been treated conventionally by the ECMO team, unless one accepts the hypothesis that three cardiothoracic surgeons can provide better intensive care than that available in the majority of UK ICUs. We do not believe this to be the case. Indeed a recent study comparing intensivists and surgeons in the management of patients with ARDS showed that management of ventilation by intensivists was associated with a trend towards improved hospital survival and fewer days of mechanical ventilation in patients who survived.<sup>79</sup> To paraphrase William of Ockham, the simplest explanation is the most likely to be true.<sup>80</sup> Namely, low volume ventilation

has been proven to improve outcome in ARDS,<sup>3</sup> but patients with such severe respiratory failure are unable to maintain homeostasis on low volume ventilation, and the use of ECMO allows non-injurious ventilator settings to be used. ECMO is merely a tool that allows lung rest.

The improvement in survival without severe disability seen in the treatment arm of the CESAR trial is an important real world outcome. It is likely that if the trial had not been designed in such a pragmatic fashion it would have failed as there were enormous changes in the NHS during the study, including inauguration and abandonment of local intensive care networks, a shift of commissioning of tertiary care services from regional health authorities to local primary care trusts, and implementation of the European working time directive legislation. The trial would also have failed owing to lack of patient recruitment if the conventional care had been protocolised, as UK intensivists could not agree protocols for national treatment when the CESAR protocol was being written. In addition, most intensivists were unwilling to consider transferring patients for conventional intensive care as they did not consider it ethical to do so.

Another important development during the study was the introduction of an arteriovenous carbon dioxide removal device (Novalung). This was used by one hospital on a patient in the conventional arm of the study, a clear protocol violation.<sup>81,82</sup> This device is not equivalent to ECMO as it provides little oxygenation. Further studies including an RCT will be needed to determine its optimal use.

The policy of ECMO in the UK involved transport to the ECMO centre. This may be hazardous for patients as seriously ill as this cohort. Indeed, five patients in the ECMO arm succumbed before they could be transferred to Glenfield. Of these, three patients died prior to transfer and two died in transit, one from catastrophic pulmonary haemorrhage and one when the oxygen supply in the ambulance failed. There were no transport deaths in the conventional arm. All the transfers were carried out by the ECMO transport team which is specifically trained and highly skilled in ground and air transfer of patients with severe respiratory failure using conventional ventilation. The ventilator used was a Pneupac Ventipac<sup>®</sup> (Smiths Group PLC, London, UK) with the addition of a PEEP valve to the breathing circuit. The team consisted of a transport nurse, who was a trained ECMO specialist, in addition to a sister/

charge nurse or senior staff nurse and an ECMO Fellow (doctor of registrar grade), both of whom had been on an in-house transport course as well as having undertaken training transports with an experienced team member until considered safe to undertake transports 'solo'. Ground ambulance was used when estimated transport time was less than 2 hours and rotary wing aircraft was used [Royal Air Force (RAF) Sea King Mk3] when a longer transport time was estimated and weather conditions allowed. Aircraft landed at the Glenfield Hospital helipad, speeding the transfer. One transport from Inverness was undertaken using a combination of ambulance, fixed wing aircraft (RAF Hercules) and helicopter. All transports were co-ordinated by the ECMO co-ordinator. It is possible that outcomes could be further improved by the implementation of a mobile ECMO patient retrieval service, as similar services have shown improved survival in patients transferred on ECMO when compared with those transferred using conventional ventilation prior to starting on ECMO at the base hospital.<sup>83,84</sup>

## Economics

CESAR was one of the first multicentre trial-based economic evaluations performed in adult critical care units in the UK. The CESAR trial was also the first RCT of adult ECMO with full economic support from the design stages of the trial, including funding for two part-time health economists, which helped the economic research team tackle many challenges in the design, methods, data collection, development and piloting of the economic questionnaire and planning of the analysis. The trial protocol was developed in collaboration with health economists, who were members of the Trial Steering Committee, and an economics working group oversaw the economic data collection and analysis.

Referral for ECMO has been shown in the CESAR trial to improve health outcomes significantly for adult patients with severe, but potentially reversible, respiratory failure when compared with CM. We have shown in this report, however, that the additional average cost per patient of treating this illness by transfer to the ECMO centre is more than double the average cost of treatment with CM. However, the lifetime prediction of cost-utility of £19,000 (\$31,000) per QALY is well within those values regarded as affordable by many health-care decision-makers. The CEA Registry, published on the World Wide Web by Tufts University

Medical School,<sup>85</sup> summarises cost–utility ratios at 2002/3 values reported in health economic evaluation studies. We have chosen some of these values to illustrate how the cost-effectiveness of ECMO compares with other health technologies in cardiovascular and respiratory medicine. For example, anticoagulation therapy with warfarin versus none is cost saving and improves health for people with atrial fibrillation;<sup>86</sup> current use of aspirin in patients with coronary heart disease aged 35–84 years costs \$11,000 per QALY gained compared with no aspirin;<sup>87</sup> and single lung transplant in end stage lung disease in the UK costs \$51,000 per QALY gained.<sup>88</sup> It is important to bear in mind when looking at such comparisons that the estimates from our model were based on highly simplified assumptions on length and quality of life for survivors, and that comparisons of cost-effectiveness are subject to many methodological pitfalls. Further detailed research would be needed to build and test a robust model that takes account of geographical location, economies of scale and scope, and long-term quality of life.

The CESAR trial was funded as part of the NIHR HTA programme, and, during the trial, access to ECMO in the UK was restricted to participants in the trial. Findings from the trial and its economic evaluation will now become key information for the UK NHS decision-makers on whether to fund ECMO for adults beyond the trial setting. Although our study was based on the largest UK study of cost functions of critical care, and compared like for like with the costs of critical care treatment across the participating units, there will also continue to be questions to resolve about any omitted costs of services (such as hospital overheads or financial ‘insurance’ costs to reflect uncertainty of predicted case load, which were not included in our cost estimates). In any business case, the final price agreed per case treated will alter the purchaser’s view of cost-effectiveness in a way that can be remodelled using the data from this study.

The findings are also relevant to other countries where ECMO is provided or being considered, although local costs, health services and practice may vary, as may travel distances (from treatment centres). Local economic models would need to be constructed to assess cost-effectiveness in different contexts.

We found that our hospital cost estimates were sensitive to critical care unit costing methods. National data on costs of NHS critical care were not available at the outset of the CESAR trial,

but are now published as tariffs for providers (NHS hospital trusts)<sup>52</sup> to use in contracts with third-party payers. A parallel research study ran alongside the trial in order to estimate the costs of patients according to the type of organ support received during their stay. Subsequent analysis demonstrated grouped numbers of organs supported on a daily basis in the critical care unit was the best predictor of the costs of care.<sup>63</sup> Although it is likely that these costs are reliable estimates of true resource costs, the NHS financial system uses different (non-case-mix adjusted) values that predict lower costs per outcome gained.

Not surprisingly, the cost-effectiveness would be improved where costs of transport and of ECMO provision could be reduced. These two factors may be inversely related. Provision of ECMO is likely to be most clinically and economically efficient (lower cost per successful case treated) in larger critical care units. It is also likely that the clinical effectiveness of smaller units would be reduced compared with busier units. However, long-distance air travel could be minimised with a larger number of well-placed critical care units, which would inevitably be smaller and less economically efficient. Almost all the air transport was provided by the RAF in the CESAR trial. This was relatively expensive, and the RAF does not aim to be a routine service provider for the NHS. Air transport costs may be reduced by implementation of a dedicated air ambulance system for patient retrieval. We would recommend further careful modelling of the most cost-effective solution for different settings.

The analysis reported here has taken the viewpoint of public sector and, especially, NHS efficiency, and so patient costs were not included in the analyses of cost-effectiveness. In the UK, health care is not a direct cost to patients as it is funded through general taxation. In other parts of the world, the additional costs would affect insurance financing. We have shown that, in the UK, costs after hospital discharge to patients and their informal carers were doubled following allocation to ECMO. Although most of these were not financial costs but voluntary time costs, there are likely to be knock-on financial and emotional effects. The costs for relatives of visiting the patient whilst in hospital were not directly measured for patients participating in the CESAR trial. However, we conducted a parallel study of costs of visiting intensive care in six participating hospitals. The results of the study in six centres in the CESAR trial suggested an average cost per single visit of around £69 at 2007

prices for out of pocket expenses. When time costs and income loss are included, the visiting cost is increased by £59 per visit. Given that the visitors interviewed were present daily with their relative or friend, the extra length of stay in the ECMO group

suggests that visiting costs would have been much higher for this group than for the CM group. More analysis from the six CESAR hospitals participating in the main survey of visiting costs will be reported elsewhere.



## Chapter 5

# Conclusions

CESAR was a pragmatic trial which has demonstrated that a strategy of transferring adult patients with potentially reversible severe respiratory failure to a single centre for consideration of ECMO treatment results in a significant reduction in mortality and/or severe disability when compared with the care received in their original hospitals. In addition, CESAR has shown that this strategy is cost-effective when compared with other high technology life saving treatments such as lung transplantation. There were over 100 patients who could not be entered into the study due to lack of beds in the ECMO centre; a potential national adult ECMO service would need to be resourced to deal with all patient referrals. This care should also allow for needs of relatives and survivors at home in addition to the hospital and formal primary care. Estimates

indicate that this would require an additional one or two ECMO centres to provide a service for England and Wales.

Future priorities for research should include:

- a long-term follow-up study of CESAR trial patients, initially at 10 years
- a national RCT of arteriovenous carbon dioxide removal (Novalung) before it becomes embedded in clinical practice
- a more sophisticated model of cost–utility, varying value of health state at baseline, using longer term follow-up data and varying geographical and other access assumptions
- an international multicentre RCT of ECMO as a treatment for respiratory failure in children.





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### Trial Steering Committee

R Adfield, E Allen, F Clemens, E Coates, N Cooper, K Diallo, D Edbrooke, D Elbourne, G Faulkner, J Fawcett, D Field, R Firmin, D Goldhill, B Gutteridge, P Hardy, S Harris, C Hibbert, S Holden, N Jones, H Killer, M Mugford, W Nganasurian, G Peek, M Pepperman, D Piercy, S Robertson, J Scott, A Tattersfield, M Thalanany, R Tiruvoipati, K Tomlin, A Truesdale, N Webster, A Wilson.

### Project management group

E Allen, F Clemens, N Cooper, K Diallo, Y Doyle, D Edbrooke, D Elbourne, G Faulkner, R Firmin, D Francis, P Hardy, S Harris, C Harvey, C Hibbert, N Jones, H Killer, M Mugford, G Peek, D Piercy, S Robertson, M Thalanany, R Tiruvoipati, K Tomlin, A Truesdale, A Wilson.

### Data co-ordinating centre, London

E Allen, F Clemens, K Diallo, D Elbourne, P Hardy, D Piercy, S Robertson, K Tomlin, A Truesdale.

### Clinical co-ordination centre, Glenfield

M Aslam, G Faulkner, R Firmin, S Harris, C Harvey, H Killer, N Jones, C McCulloch, G Peek, J Redfern, R Reeves, N Roberts, A Sheward, L Smith, A Sosnowski, A Tebbat, R Tiruvoipati.

### Economic evaluation

E Coates, N Cooper, V Knights.

### Data Monitoring Committee

D Altman, R Doll (died 2005), T Evans, D Macrae.

### Follow-up group

J Sanderson-Mann, P Sinfield, C Tarrant, H Watkinson, A Wilson.

### Randomisation service

G McPherson, A Walker.

### IT support

M Bennett, A King.

### Independent categorisation of causes of deaths

C Waldmann, D Goldhill.

### Recruiting centres and named collaborating doctors and nurses

Numbers in parentheses denote the number of patients recruited by that centre:

Airedale General Hospital (2), J Scriven, K Price; Alexandra Hospital (1), T Leach, D Bagnall, L Clements; Arrowe Park Hospital (1), J Chambers, P Grice, C Taylor; Ayr Hospital (6), I Taylor, M Dunlop, D Kerr; Bassetlaw District General Hospital (1), R Harris, W Lee, P Wootton; Bedford Hospital (10), D Niblett, F Barchard, F Bertasius; Castle Hill Hospital (8), S Gower, J Dickson, K Roberts; Cheltenham General Hospital (2), W Doherty, A Culpepper, S Maisey; Chesterfield & North Derbyshire Royal Hospital

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## Contribution of authors

Giles Peek (Consultant in Cardiothoracic Surgery and ECMO) was the lead clinical investigator for the CESAR trial. He was involved in the design and conduct of research and the interpretation and reporting of results, and was a member of the project management team. Diana Elbourne (Professor of Healthcare Evaluation) was the lead investigator for statistics and trial design and management for the CESAR trial and was involved in design and conduct of research, the

project management team and Data Monitoring Committee, and interpretation and reporting of results. Miranda Mugford (Professor in Health Economics) was the lead investigator for economics input to the CESAR trial, involved in design and conduct of economics research, and interpretation and reporting of results; she was also a member of the project management team. Ravindranath Tiruvoipati (Clinical Research Fellow) was involved in the recruitment of centres and patients, the clinical conduct of research, the project management team, and the interpretation and reporting of results. Andrew Wilson (Professor of Primary Care Research) was the lead investigator for the follow-up of participants in the CESAR trial, involved in the design and conduct of research, the project management team, and interpretation and reporting of results. Elizabeth Allen, Felicity Clemens and Pollyanna Hardy (Lecturers in Medical Statistics) were all involved in the design and conduct of research, the project management team, and interpretation and reporting of results. Richard Firmin (Consultant in Cardiothoracic Surgery, Director of ECMO Services) was an investigator for the CESAR trial and a member

of the project management team, and involved in design and conduct of research, and interpretation and reporting of results. Clare Hibbert (Health Economics Research Fellow) was an investigator for economics input to the CESAR trial and a member of the project management team, and involved in design and conduct of economics research, and interpretation and reporting of results. Nicky Jones (Clinical Research Fellow) was involved in recruitment of centres and patients and clinical conduct of research, and was a member of the project management team. Hilliary Killer (ECMO Unit Manager) was a member of the project management team. Mariamma Thalanany (Health Economics Researcher) was an investigator for economics input to the CESAR trial and a member of the project management team, and involved in design and conduct of economics research, and interpretation and reporting of results. Ann Truesdale (Trials Adviser) was involved in design and conduct of research, recruitment of centres, ethics approvals, data management, and interpretation and reporting of results, and was a member of the project management team.





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### Observers

<p>Ms Kay Pattison Senior NIHR Programme Manager, Department of Health</p>	<p>Mr Simon Reeve, Head of Clinical and Cost- Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health</p>	<p>Dr Heike Weber, Programme Manager, Medical Research Council</p>	<p>Dr Ursula Wells, Principal Research Officer, Department of Health</p>
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## Psychological and Community Therapies Panel

### Members

<p><b>Chair,</b> <b>Professor Scott Weich,</b> Professor of Psychiatry, University of Warwick</p> <p>Professor Jane Barlow, Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School</p> <p>Dr Sabyasachi Bhaumik, Consultant Psychiatrist, Leicestershire Partnership NHS Trust</p> <p>Mrs Val Carlill, Service User Representative, Gloucestershire</p>	<p>Dr Steve Cunningham, Consultant Respiratory Paediatrician, Lothian Health Board</p> <p>Dr Anne Hesketh, Senior Clinical Lecturer in Speech and Language Therapy, University of Manchester</p> <p>Dr Yann Lefevre, GP Partner, Burrage Road Surgery, London</p> <p>Dr Jeremy J Murphy, Consultant Physician &amp; Cardiologist, County Durham &amp; Darlington Foundation Trust</p> <p>Mr John Needham, Service User, Buckinghamshire</p>	<p>Ms Mary Nettle, Mental Health User Consultant, Gloucestershire</p> <p>Professor John Potter, Professor of Ageing and Stroke Medicine, University of East Anglia</p> <p>Dr Greta Rait, Senior Clinical Lecturer and General Practitioner, University College London</p> <p>Dr Paul Ramchandani, Senior Research Fellow/Cons. Child Psychiatrist, University of Oxford</p>	<p>Dr Howard Ring, Consultant &amp; University Lecturer in Psychiatry, University of Cambridge</p> <p>Dr Karen Roberts, Nurse/Consultant, Dunston Hill Hospital, Tyne and Wear</p> <p>Dr Karim Saad, Consultant in Old Age Psychiatry, Coventry &amp; Warwickshire Partnership Trust</p> <p>Dr Alastair Sutcliffe, Senior Lecturer, University College London</p> <p>Dr Simon Wright, GP Partner, Walkden Medical Centre, Manchester</p>
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### Observers

<p>Ms Kay Pattison Senior NIHR Programme Manager, Department of Health</p>	<p>Dr Morven Roberts, Clinical Trials Manager, MRC, London</p>	<p>Professor Tom Walley, HTA Programme Director, Liverpool</p>	<p>Dr Ursula Wells, Policy Research Programme, DH, London</p>
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## Expert Advisory Network

### Members

Professor Douglas Altman,  
Professor of Statistics in  
Medicine, Centre for Statistics  
in Medicine, University of  
Oxford

Professor John Bond,  
Professor of Social Gerontology  
& Health Services Research,  
University of Newcastle upon  
Tyne

Professor Andrew Bradbury,  
Professor of Vascular Surgery,  
Solihull Hospital, Birmingham

Mr Shaun Brogan,  
Chief Executive, Ridgeway  
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,  
Chief Executive, Regulation  
and Improvement Authority,  
Belfast

Ms Tracy Bury,  
Project Manager, World  
Confederation for Physical  
Therapy, London

Professor Iain T Cameron,  
Professor of Obstetrics and  
Gynaecology and Head of the  
School of Medicine, University  
of Southampton

Dr Christine Clark,  
Medical Writer and Consultant  
Pharmacist, Rossendale

Professor Collette Clifford,  
Professor of Nursing and  
Head of Research, The  
Medical School, University of  
Birmingham

Professor Barry Cookson,  
Director, Laboratory of Hospital  
Infection, Public Health  
Laboratory Service, London

Dr Carl Counsel, Clinical Senior Lecturer in  
Neurology, University of  
Aberdeen

Professor Howard Cuckle,  
Professor of Reproductive  
Epidemiology, Department  
of Paediatrics, Obstetrics &  
Gynaecology, University of  
Leeds

Dr Katherine Darton,  
Information Unit, MIND – The  
Mental Health Charity, London

Professor Carol Dezateux,  
Professor of Paediatric  
Epidemiology, Institute of Child  
Health, London

Mr John Dunning,  
Consultant Cardiothoracic  
Surgeon, Papworth Hospital  
NHS Trust, Cambridge

Mr Jonothan Earnshaw,  
Consultant Vascular Surgeon,  
Gloucestershire Royal Hospital,  
Gloucester

Professor Martin Eccles,  
Professor of Clinical  
Effectiveness, Centre for Health  
Services Research, University of  
Newcastle upon Tyne

Professor Pam Enderby,  
Dean of Faculty of Medicine,  
Institute of General Practice  
and Primary Care, University of  
Sheffield

Professor Gene Feder,  
Professor of Primary Care  
Research & Development,  
Centre for Health Sciences,  
Barts and The London School  
of Medicine and Dentistry

Mr Leonard R Fenwick,  
Chief Executive, Freeman  
Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher,  
Antenatal Teacher and Tutor  
and President, National  
Childbirth Trust, Henfield

Professor Jayne Franklyn,  
Professor of Medicine,  
University of Birmingham

Mr Tam Fry,  
Honorary Chairman, Child  
Growth Foundation, London

Professor Fiona Gilbert,  
Consultant Radiologist and  
ACRN Member, University of  
Aberdeen

Professor Paul Gregg,  
Professor of Orthopaedic  
Surgical Science, South Tees  
Hospital NHS Trust

Bec Hanley,  
Co-director, TwoCan Associates,  
West Sussex

Dr Maryann L Hardy,  
Senior Lecturer, University of  
Bradford

Mrs Sharon Hart,  
Healthcare Management  
Consultant, Reading

Professor Robert E Hawkins,  
CRC Professor and Director  
of Medical Oncology, Christie  
CRC Research Centre,  
Christie Hospital NHS Trust,  
Manchester

Professor Richard Hobbs,  
Head of Department of Primary  
Care & General Practice,  
University of Birmingham

Professor Alan Horwich,  
Dean and Section Chairman,  
The Institute of Cancer  
Research, London

Professor Allen Hutchinson,  
Director of Public Health and  
Deputy Dean of ScHARR,  
University of Sheffield

Professor Peter Jones,  
Professor of Psychiatry,  
University of Cambridge,  
Cambridge

Professor Stan Kaye,  
Cancer Research UK Professor  
of Medical Oncology, Royal  
Marsden Hospital and Institute  
of Cancer Research, Surrey

Dr Duncan Keeley,  
General Practitioner (Dr Burch  
& Pttrs), The Health Centre,  
Thame

Dr Donna Lamping,  
Research Degrees Programme  
Director and Reader in  
Psychology, Health Services  
Research Unit, London School  
of Hygiene and Tropical  
Medicine, London

Mr George Levy,  
Chief Executive, Motor  
Neurone Disease Association,  
Northampton

Professor James Lindesay,  
Professor of Psychiatry for the  
Elderly, University of Leicester

Professor Julian Little,  
Professor of Human Genome  
Epidemiology, University of  
Ottawa

Professor Alistaire McGuire,  
Professor of Health Economics,  
London School of Economics

Professor Rajan Madhok,  
Medical Director and Director  
of Public Health, Directorate  
of Clinical Strategy & Public  
Health, North & East Yorkshire  
& Northern Lincolnshire  
Health Authority, York

Professor Alexander Markham,  
Director, Molecular Medicine  
Unit, St James's University  
Hospital, Leeds

Dr Peter Moore,  
Freelance Science Writer,  
Ashted

Dr Andrew Mortimore,  
Public Health Director,  
Southampton City Primary  
Care Trust

Dr Sue Moss,  
Associate Director, Cancer  
Screening Evaluation Unit,  
Institute of Cancer Research,  
Sutton

Professor Miranda Mugford,  
Professor of Health Economics  
and Group Co-ordinator,  
University of East Anglia

Professor Jim Neilson,  
Head of School of Reproductive  
& Developmental Medicine  
and Professor of Obstetrics  
and Gynaecology, University of  
Liverpool

Mrs Julietta Patnick,  
National Co-ordinator, NHS  
Cancer Screening Programmes,  
Sheffield

Professor Robert Peveler,  
Professor of Liaison Psychiatry,  
Royal South Hants Hospital,  
Southampton

Professor Chris Price,  
Director of Clinical Research,  
Bayer Diagnostics Europe,  
Stoke Poges

Professor William Rosenberg,  
Professor of Hepatology  
and Consultant Physician,  
University of Southampton

Professor Peter Sandercock,  
Professor of Medical Neurology,  
Department of Clinical  
Neurosciences, University of  
Edinburgh

Dr Susan Schonfield,  
Consultant in Public Health,  
Hillingdon Primary Care Trust,  
Middlesex

Dr Eamonn Sheridan,  
Consultant in Clinical Genetics,  
St James's University Hospital,  
Leeds

Dr Margaret Somerville,  
Director of Public Health  
Learning, Peninsula Medical  
School, University of Plymouth

Professor Sarah Stewart-Brown,  
Professor of Public Health,  
Division of Health in the  
Community, University of  
Warwick, Coventry

Professor Ala Szczepura,  
Professor of Health Service  
Research, Centre for Health  
Services Studies, University of  
Warwick, Coventry

Mrs Joan Webster,  
Consumer Member, Southern  
Derbyshire Community Health  
Council

Professor Martin Whittle,  
Clinical Co-director, National  
Co-ordinating Centre for  
Women's and Children's  
Health, Lymington



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***We look forward to hearing from you.***