HESG Conference, Newcastle June 2005

Methods for economic evaluation alongside a national, multicentre trial in the UK: Conventional ventilation or ECMO for Acute Respiratory Disease Syndrome (CESAR)

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CESAR is a collaborative work between the Glenfield Hospital, Leicester; Medical Statistics Unit, London School of Hygiene and Tropical Medicine; University of East Anglia, Norwich; SCHARR, University of Sheffield, and University of Leicester.

The Trial (ISRCTN47279827) is funded by the NHS R&D Health Technology Assessment programme (HTA). The opinions expressed here are those of the author(s) and not necessarily those of the UK Government's Department of Health or the Sponsor".

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Introduction

The acute respiratory disease syndrome (ARDS) is an acute and progressive respiratory disease associated with high mortality of about 50-70% (Esteban et al 2000; Varon & Wenke1997). Conventional treatment for ARDS is mechanical ventilation with high level oxygen. Extracorporeal membrane oxygenation (ECMO) is a technique which uses a life support circuit to temporarily take over the gas exchange function of the lung outside the body, obviating the need for gas exchange in the lungs, and thereby allowing the lungs to rest and recover (Hemilla et al 2004).

ECMO has been shown to be life saving in neonates with respiratory failure (Roberts 1998); however its usefulness in adults remains to be proven with two randomised controlled trials (Zapol et al 1979; Morris et al 1994) failing to show any effectiveness of ECMO over conventional treatment. Both ECMO and conventional treatment have undergone many refinements since these studies were published and better outcomes for adults treated with ECMO have been reported in uncontrolled studies (ELSR 1995, Peek et al 1997, Hemmila et al 2004). However, the question, whether the improved ECMO can really challenge the advanced conventional treatment of adult ARDS can be best answered by a randomised controlled trial since this is currently the most robust method of comparing the effectiveness of new technologies against current practice.

Assessment of effectiveness alone, however, is unlikely to determine whether new technologies make best use of available resources. As an expensive technology with substantial start up and capital costs in addition to the uncertainty surrounding its outcome in adults, ECMO makes a good case for an economic evaluation to determine its cost-effectiveness against conventional treatment. In addition, a literature search failed to find any studies that had investigated the cost-effectiveness of ECMO in adults. The CESAR Trial (Conventional ventilation or ECMO for Acute Respiratory Disease Syndrome) was set up to evaluate the effectiveness and cost-effectiveness of ECMO for adults with funding for the trial from the NHS R&D Health Technology Assessment programme and costs of ECMO treatment provided by the National Specialist Commissioning Advisory Group.

The purpose of this paper is to describe and justify the methods used for economic evaluation of the trial. In our view it is important to record our methods in detail before publication of the results of the trial so that a record of detail not normally found in the final trial reports can be made available in the public domain. The economic evaluation adopted the best methods and guidelines which were available at the time of designing the trial. Since that time there have been many developments in methods for economic evaluation and in the methods for analysing cost data

(Drummond & McGuire 2001). Where possible, these new developments have been incorporated into the design of the economic evaluation and into the planned analysis of economic data.

Background to the trial

Acute respiratory distress syndrome (ARDS), occur with incidences of 1.5 – 13.5/100,000 inhabitants per year (Luhr et al 1999) worldwide. In the UK, an estimated 350 adults develop severe, but potentially reversible respiratory failure every year. In spite of significant advances in the understanding of the pathophysiology of ARDS in recent years and consequent improved treatment methods in specialist centres, the mortality from ARDS in adults remains high at 50 to 70% (Esteban et al 2000; Varon & Wenke 1997) with enormous human and financial costs.

Extracorporeal membrane oxygenation (ECMO) was developed as a supportive therapy for severe respiratory failure and was introduced into treatment of severe acute ARDS in the 1970s (Lewandowski 2000). The technique of ECMO involves placing patients on a life support circuit to temporarily take over the gas exchange function of the lung to allow the lung to rest and recover Hemmila et al 2004).

Evidence of ECMO in adults

Evidence of effectiveness of ECMO for adults with severe acute respiratory failure (ARDS) remains unclear and controversial. Two large randomized controlled trials (RCTs) published in 1979 and 1994 failed to show an advantage of ECMO over conventional treatment (Zapol et al 1979; Morris et 1994). However, in July 1995, the Extracorporeal Life Support Organization Register in USA recorded an overall survival rate of 41% in 197 adult ARDS patients treated with extracorporeal respiratory support (ELSR 1995). In Europe, survival data of ECMO treated ARDS patients collected over 7 years (1992 to 1999) showed survival rates of around 50%. Similarly, ECMO survival rates in excess of 50% have been reported in uncontrolled studies (Peek et al 1997, Hemmila et al 2004).

Evidence of ECMO in neonates

The registry of the Extracorporeal Life Support Organization (Tracy et al 2000) has reported an 80% survival rate in 10391 patients with neonatal respiratory failure who were treated with ECMO from 1980 to 1995. In the UK, a randomised controlled trial of ECMO for neonates born with respiratory failure convincingly demonstrated the effectiveness of ECMO in improving patient survival without severe disability (Roberts 1998). The survival rates were 68% and 41% in the ECMO and control arms respectively. Neonatal ECMO in the UK is now a supra-regional service receiving central funding.

Long-term recovery and quality of life
(a) With conventional treatment

Hopkins et al (1999) reported on long-term outcome of 55 consecutive patients and found that, at hospital discharge, 100% exhibited cognitive and affective impairments, as well as problems with health status that affected their quality of life. One year after ARDS, 30% of the patients still showed generalized cognitive decline. A one-year follow-up study by Herridge et al (2003) reported persistent functional disability in ARDS survivors with only 49% returning to work and a two-year follow-up study by Hopkins et al (2004) found significant neurocognitive and emotional morbidity and decreased quality of life in survivors. Similarly, Kapfhammer et al (2004) reported that long-term survivors of ARDS face a major risk of post traumatic stress disorder and major impairments in health-related quality of life.

(b) With ECMO

Few authors have investigated the long-term morbidity of ARDS patients treated with ECMO. A retrospective study of 38 young survivors by Knoch *et al* (1992) found that within 12-20 months after discharge, 36 out of the 38 patients had returned to normal working and social activities.

Evidence of cost-effectiveness

A detailed literature search failed to find any economic evaluation studies of Adult ECMO. However, Morris et al (1994) has reported estimated costs for the treatment of ARDS as (USA $120,800 or UK £75,500) per patient with ECMO and (USA $97,200 or UK £60,750) per patient with conventional treatment. And, a cost-effectiveness study of providing rather than withholding mechanical ventilation and intensive care for patients with ARDS (Hamel et al 2000) reports that for low-risk patients the incremental cost (1998 US dollars) per quality-adjusted life-year saved by providing rather than withholding ventilator support and aggressive care was $29,000. For medium-risk patients the incremental cost-effectiveness was $44,000 per QALY, and for high-risk patients it was $110,000 per QALY.

The only economic evaluation of ECMO was the UK collaborative randomised trial of neonatal ECMO (Roberts 1998) which reported the estimated additional cost (UK 1994-95 price) of ECMO per additional surviving infant without severe disability as £51,222 and the cost per surviving infant with no disability as £75,327. Follow-up at 4 years for the same study show the incremental cost (UK 2001 price) of neonatal ECMO to be £16,707 per life year gained and £24,775 per disability-free life year gained (Petrou & Edwards 2004).

Rationale for Economic evaluation of the CESAR Trial

Based on the evidence that has been reported so far on the effectiveness of ECMO and the lack of economic evaluation of ECMO in adults, it is clear that there is an urgent need to ascertain the cost-effectiveness of ECMO against the conventional treatment of adult ARDS. This answer is best provided by an economic evaluation alongside a randomized, controlled trial. The economic evaluation is justified as (1) ECMO is perceived to be an expensive technology with huge resource consequences however its costs in adults have never been compared against usual treatment, (2) ECMO is practiced in many centres in many western countries as shown by the many published uncontrolled studies yet its effectiveness has not been proven in a randomised controlled trial (3) though the population affected is small the expected improvements in terms of additional life years and quality of life are quite high. A policy decision on whether or not to provide ECMO for adults suffering from ARDS is therefore necessary.

The CESAR trial is the first randomised controlled trial of adult ECMO with an economic evaluation incorporated into the design of the trial. The trial will help define the best cost-effective treatment for adults with severe ARDS so that rational treatment and health service planning can be made in their best interests.

The Trial

The CESAR trial is a randomised controlled trial (recruiting patients between 2001-2006) comparing two alternative strategies for treating ARDS in adults: conventional management, which can include any treatment modality thought appropriate by the patient's intensivist, and ECMO. All intensive care units (ICUs) in the UK can take part and 96 units have registered with the trial. The participation of so many ICUs is necessary due to the small numbers of adults who suffer from the condition annually (350 adults per year). The end point of intervention is discharge from the ECMO unit and follow-up duration is 6 months post-randomisation.

The Intervention: ECMO is provided at Glenfield Hospital, Leicester,UK which has several years of experience of providing ECMO. Conventional treatment is provided by centres acknowledged by a sub-group of the Intensive Care Society to be capable of providing an appropriately high standard of conventional care for ECMO-eligible patients. In addition to the these centres patients meeting ECMO entry criteria may be entered into the trial from other hospitals referred to as referral hospitals (RH) if these hospitals are prepared to transfer the patient to a designated conventional treatment centre (CTC) should the allocation be to conventional management.

Transport: Patients randomised to conventional treatment and who are in a designated CTC at time of recruitment do not need transport. All patients from referral hospitals randomised to ECMO or conventional treatment and all patients randomised to ECMO are transferred to their respective treatment centres by the Glenfield transport team. Depending on the severity of the patient's condition and distance road or air ambulance may be used. If the transport team decided that it is not safe to move a patient then the patient remains in the original unit until he/she is safe to be transferred, recovered or died. Such outcomes are analysed as part of the treatment option to which the patient was randomised (intention to treat). There is no crossover to ECMO for patients allocated to conventional management. If a patient's condition altered (prior to start of treatment) such that ECMO was no longer possible or appropriate then ECMO is not initiated. Such patient's outcome is analysed as part of ECMO group (intention to treat).

Due to the nature of the intervention, it is not possible for either the trial participants or the recruiting centres to be blinded to the allocation group of study participants. However, interviewers at follow-up are blinded to the allocation group of participants.

Sample size, study population, eligibility, outcome measures and ethics: Power calculation based on current mortality rates of adult ARDS shows that a sample size of 180 would have sufficient power to detect a reduction in primary outcome by a third (based on 5% statistical significance (2-sided test) and 80% power).

Adult patients (18-65 years) with severe, but potentially reversible respiratory failure (defined as a Murray score ≥3.0, or uncompensated hypercapnoea with a pH<7.20) are eligible for inclusion in the trial. Patients are excluded if they had high pressure and/or high FIO_2 ventilation > 7 days, had intra-cranial bleeding, or any other contra-indication to limited heparinisation or to continuation of active treatment.

The primary outcome measure is increase in survival without severe disability at six months. Secondary outcome measures include: duration of ventilation, length of ICU stay, length of hospital stay, activities of daily living, quality of life, respiratory symptoms, psychological state, uptake of health services, and household resources.

Multi-centre ethics approval was obtained from Trent MREC followed by local ethics approval (LREC) and R&D approval for every participating centre.

The economic question

The economic evaluation addresses the question of economic efficiency or value for money of the alternative treatment options. The economic question asks "what are the costs and benefits associated with ECMO and is it cost-effective from a societal perspective"?

The objectives of the economic evaluation are:

- To compare the costs of ECMO with those of conventional treatment provided for the treatment of ARDS in adults
- To assess the cost-effectiveness of ECMO compared with conventional treatment in terms of additional survival with and without disability at six months post-randomisation.
- To assess the cost-utility of ECMO compared with conventional treatment in terms of utility gain as measured by EQ5D measured at 6 months follow-up.

These aims will allow researchers to address the primary hypothesis which is that ECMO will be cost effective from the viewpoint of the National Health Service and society compared to conventional treatment. If the results of this trial favour the management of ECMO for patients with ARDS it is also important to consider further options for provision of ECMO in the UK.

Design of Economic Evaluation alongside the CESAR Trial

The design of an economic evaluation is crucial to the production of valid and reliable economic data. The economic evaluation alongside the CESAR trial is designed on published recommendations (Drummond et al 1997) and involves a number of steps such as deciding the: type of economic evaluation, the comparator, perspective, time horizon, outcome measures, identification, measurement and valuation of resources, estimation of unit costs and an analysis plan which includes decisions on discounting future costs and consequences, tackling uncertainties and presentation of results. These steps are described below along with the decisions taken for the design of the CESAR Trial.

Type of economic evaluation, comparator, perspective and time horizon

The evaluation is designed as (1) a cost-effectiveness analysis (CEA) with increase in survival without severe disability at six months as the main outcome measure and (2) a cost-utility analysis (CUA) where the outcome measure is the utility value obtained from EQ5D measured at 6 months follow-up. The ideal comparator for any economic evaluation is the one which is the most commonly used treatment for the condition being evaluated and for the CESAR trial the comparator is conventional ventilatory support - the current best treatment for adult ARDS.

The gold standard perspective for economic evaluations is the societal perspective (Gold et al 1996). For the CESAR trial the perspectives includes societal as well as those of the National Health Service, and household so that the final published results will be beneficial to decision makers who may be making decisions under different constraints.

The time horizon or follow-up duration must ideally be long enough to capture all the important clinical and economic consequences of the intervention under evaluation (Gold et at 1996). Practical considerations should also be taken into account such as the cost of running the trial and the need to minimise sample attrition. The follow-up duration for this trial is 6 months. This may not allow the full cost and benefits to be measured. Modelling long-term costs and effects, though not a primary aim in this trial, may become possible at a future date.

Outcome measures for economic evaluation

1. Health related quality of life (measured using EQ5D)
2. Survival without severe disability - interview at 6 months.

Cost estimation in economic evaluation

The total societal cost related to any treatment programme consists of the following components: costs of providing the treatments under evaluation, costs of other health care resources used (hospitalisation, tests, procedures, drugs, visits to family doctor, out patient visits etc); costs of non-health resources, costs to patients and family and productivity costs. Cost estimation involves three stages: identifying, measuring and valuing resources.

Identifying resource use - Identification consists of listing all the resources that may be affected by an intervention as comprehensively as possible with regards to the chosen perspective. For the CESAR trial all aspects of resource use considered to be relevant for the two treatment options were identified using expert medical advice. A selection of these is given in Appendix I, and include resource use associated with initial stay in the ICU, use of ambulance, stay in other hospital wards before discharge, resource use related to patient's death in the hospital, costs of visiting incurred by relatives whilst patients are in hospital, resource use after discharge up to six months, major changes in household, out-of-pocket expenses of patient and family, loss of paid and unpaid working time, changes in working time, informal care, and government grants & benefits.

Measuring resource use - The usual method is to quantify resource use in terms of number of inpatient days, outpatient visits and so on and collect these either prospectively or retrospectively through the use of questionnaires, interviews, hospital records etc. In the CESAR trial, data is

collected prospectively from every trial participant at various points of his/her progress from recruitment to the follow-up at 6-months using a series of questionnaires. The questionnaires are listed below with details of who administers each questionniare and what it collects.

a) Daily organ support form - completed by intensive care staff for each patient in the trial on a daily basis to obtain resources used during the ECMO/Conventional treatment period.
b) Transport form 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 (2) – completed by Glenfield transport team to record ambulance journey of participants returning to the original recruiting hospital after ECMO.
d) Outcomes data sheet - completed by the relevant medical staff to obtain number of in-patient days in that hospital, date on death of patient (if applicable), date of discharge, date of transfer to another hospital/home, use of ambulance for transfer etc
e) Memory aid– to be completed and kept by every participant to documents all services used from discharge to follow-up to help them to answer questions at 6 months.
f) Patient cost questionnaire - administered by trained interviewer at the patient's home or by telephone to collect resource use data from discharge to 6 months post-randomisation for those patients who survived.
g) GP proforma - completed by GPs to collect resource use of those patients who refuse the 6-month follow-up but who give consent to obtain their resource use from GP records.

The patient's memory aid (e) and the Patient cost questionnaire (f) were piloted with five patients discharged from the ICU of Glenfield Hospital, Leicester and the GP proforma (g) piloted with 5 general practitioners. Follow-up interviewers were trained in the administration of the 6-month follow-up questionnaire. As it was anticipated that Ambulance trusts across the UK may at some point be involved in the transport of a CESAR patient a list of all the Ambulance trusts in UK was made and participation from every ambulance trust was secured within 2 months of the start of the trial.

Two items of resource use which are not collected alongside the trial are (1) resource use associated with a patient's death in ICU and (2) resource use incurred by relatives whilst visiting patients in intensive care/ hospital stay. These items are excluded due to the practical difficulty of collecting these from the 96 centres in the trial and due to the lack of a well defined methodology. However, cost of visiting is being estimated by a separate study using a sample of CESAR centres but not necessarily visitors of patients in the CESAR trial and is described in more detail under "estimating unit costs".

Data collection

Following recruitment, the progress of all participants is tracked until their discharge from hospital so that resource use can be accurately measured and collected at each stage. During the initial treatment period (ECMO or conventional ventilation) data is collected on number of organs supported and the level of organ support on a daily basis. After transfer to another hospital or another ward within the same hospital after the acute phase of the illness, resource use is measured as total number of in-patient days up to discharge.

Details of all ambulance use at recruitment (patients randomised to ECMO and patients who have to be moved to a conventional treatment centre) are collected by the Glenfield transport team and details of all other ambulance journeys for example transfer between hospitals are collected by the relevant hospitals and sent to the research team. Data collected include date, time, origin and destination of journey, mode of transport (road ambulance, fixed wing aircraft, or helicopter), duration of journey, and distance travelled by patient.

After discharge from hospital, each participant is sent details of the follow-up interview and a 'memory aid' to record use of resources up to the follow up. A series of options are given for follow-up (1) face-to-face home interview (2) telephone interview (3) postal questionnaire and (4) collection of resource use from GP records. Those who choose option (4) are requested to send back a signed consent form. Those patients still in hospital at six months are interviewed at their hospital bedside using a very short resource use questionnaire.

Valuing resource use / Estimating unit costs

In order to estimate total cost of treatment for each trial participant, the respective quantities of resource use is multiplied by their corresponding unit cists. Unit costs for resources used are obtained from a variety of sources. Some resources used by participants are in the form of total outlay figures for each item and therefore does not need unit costs to value them. For example, cost of ambulance journeys by trial patients are obtained directly from the relevant ambulance trusts/air ambulance providers and incorporates all overhead and running costs and private costs reported by participants and their family. The unit costs of most items of resource use are obtained from nationally available sources (Curtis & Netten 2004; NHS Reference costs). The cost of drugs prescribed by general practitioners is obtained from the *British National Formula* (www.bnf.org) Informal care is valued by the opportunity cost method suggested by Posnett & Jan (1996). An average cost per day for each level of ECMO or conventional care is derived from estimates from a separately funded study (HRG study to be published soon) and weighted/adjusted for each centre in

the CESAR trial. Cost of visiting is also derived from a separate study. Details of both studies are given below. Table 1 lists the sources for all unit costs used for valuation.

Table 1: Sources of unit costs

Category of costs	UNIT Cost Source
ICU costs	• Estimated separately (see below)
Resources used after discharge	• PSSRU (Curtis & Netten 2004) • NHS reference costs http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en • British National Formulary (www.bnf.org)
Personal/ household travel Out-of-pocket expenses	• Automobile Association (AA) motoring costs. http://www.theaa.com/allaboutcars/advice/advice_rcosts_home.html • Directly reported by participants (Unit costs not needed)
Informal care	• Estimated separately (see below)
Ambulance costs Major household costs	• Ambulance trusts (unit costs not needed) • Reported by participants
Cost of visiting	• Estimated from separate study (see below)

Estimation of unit costs for ICU stays, visiting the ICU and informal care deserves a special mention as these are derived by separate costing exercises. These are summarised below.

(1) ICU Costing (HRG study to be published soon)

This study estimated an average daily cost for ICU by collecting data on the annual expenditure of intensive care units and apportioning this sum by their annual throughput of patients. Seventy critical care units and hospital finance departments were sent questionnaires to document their 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), 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 was also collected on number of patient days, no of staffed beds, no of patient admissions, type of critical care (ICU, HDU) etc. An average daily cost was calculated by using the following formula:

$$\sum \frac{\text{Annual expenditure on Staff + Consumables + Clinical Support Services}}{\text{Annual number of total patient days}}$$

To adjust the average daily cost to reflect the severity of illness or degree of organ support required by patients a weighting is required. Weights were produced using level of care and organ system support data collected as part of the Critical Care National Healthcare Resource Group (HRG) study. A total cost of ICU stay for each patient was calculated by weighting patients' average daily cost according to the respective configuration of organs supported on a daily basis and then adding these up to produce a total cost.

Not all CESAR centres took part in the HRG study. Separate visits were made to these centres including the ECMO centre to collect the same data as in the HRG study in order to estimate the daily cost in the same way.

(2) Costs of visiting patients in intensive care

This study is currently ongoing in nine intensive care units in the UK which are all registered with the CESAR trial to estimate the average cost of visiting patients in intensive care. All adults visiting the intensive care units during a three-week duration are requested to complete a questionnaire that asks them about their time spent in visiting and travel, out-of-pocket expenses, employment status, loss of income etc. The data obtained will be used to estimate the average cost of visiting per day. A pilot study of the costs of visiting (to be soon published) was carried out in Dec/Jan 2002 at an ICU in the UK and the following mean costs estimated: mean cost of time foregone - £46.21/day; mean out-of-pocket expenses - £29.30/day and mean lost wages - £50.72/day. Time was valued along the lines suggested by Posnett & Jan 1996. Automobile Association (AA) published costs was used to estimate the cost per mile of private car. The multi-centre study will estimate cost of time and private costs along similar lines. The multi-centre study will be completed by November 2005.

(3) Valuation of informal care time

From a societal perspective, the value of informal care may be recognised by considering the cost of its replacement. From the perspective of the individual carer, the opportunity cost of caring may be understood in terms of the alternatives forgone as a result of taking on this role which may include: employment opportunities; other unpaid work, such as caring for other family members; and leisure activities, including holidays, social activities and relaxation.

In the CESAR trial, informal time will be valued according to Posnett & Jan's (1996) scenarios: working time were 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 were unpaid housework is not replaced. Average wage rates of mean and women in

the United Kingdom needed for estimating time costs will be obtained from Office of National Statistics data set (http://www.statistics.gov.uk/).

Analysis and reporting of cost data – Planned methods

The existence of patient level data on both costs and effects of interventions generated by economic evaluations conducted prospectively alongside clinical trials have led to increased use of statistical methods to analyse the data. Methodological development of statistical methods over the last decade has been rapid with many alternative techniques having been suggested for economic evaluation (Briggs 2003). As a result recent literature on the topic of statistical methods for cost-effectiveness analysis is something of a minefield with many state of the art techniques so that what was once considered acceptable in terms of analysis is no longer considered sufficient. However, there is also a need to analyse and present results in a simple format for the benefit of groups not yet conversant with the state of the art techniques.

The planned methods for analysis of cost data are based on best methods recommended in Drummond & McGuire (2001) and Briggs (2003). The analysis will be conducted from three different viewpoints, namely: (1) The health care provider's viewpoint (NHS) (2) The patient and/or household's viewpoint and (3) The societal viewpoint. Mean, medians and standard deviations of costs will be available. Sensitivity analysis and statistical tests will be employed to test the uncertainty in the results. Key assumptions, items of resource use which is shown to bring about a significant cost difference, unit costs, cost of resources, use of air ambulance and variability in outcomes will be subject to sensitivity testing. Bootstrap technique will be used for estimating the probability distribution of the cost-effectiveness ratio and its confidence intervals. Resources and costs will be measured in the year in which they occur using appropriate unit costs for each year of resource use.

The analysis and reporting will involve the following:

1. Complete list of all reported use of resources, unit costs used for valuation of resources; sources of unit costs and where unit costs were estimated a clear description of the methods ('raw data').

2. Total costs/patient & descriptive statistics (**Table 2**) - A total cost will be calculated for each trial participant by multiplying all resources used by each participant by the respective unit costs. From this, the mean ,median, range, standard deviation and quantiles of costs will be estimated for each of the above mentioned perspectives.

Table 2: Costs of health care per patient

	ECMO			CM			Difference in cost
	Mean	Median	Range	Mean	Median	Range	
1. Health care costs from trial entry to 6 months (1.1 + 1.2 + 1.3)							
1.1 Costs of initial hospital care							
1.2 Costs of resource use from discharge to 6 months							
1.3 Costs of ambulance							
2. Private health care costs							
2.1 Reported health care costs							
2.2 Estimated health care costs							
3. Cost of informal care							
4. Total health care costs - costs of initial care + private costs + informal care (1 + 2 +3)							

3. Incremental cost-effectiveness ratio (ICER) (**Table 3**) - Incremental analysis involves calculating the ratio of the additional benefits to additional costs ie how much more it costs to achieve a given improvement in outcomes relative to the comparator. This is called the incremental costs-effectiveness ratio (ICER) and can be written as follows:

$$\text{ICER} = \frac{\text{Difference in costs}}{\text{difference in outcomes}}$$

The ICER will be presented on the cost-effectiveness plane which will show areas of rejection, dominance or uncertainty.

Table 3: Incremental cost-effectiveness ratios

	Mean	Confidence intervals
Health care provider's view point		
Difference in cost per patient (excluding patient costs)		
Difference in quality adjusted survival		
Difference in EQ5D QALYs at 6 months		
Incremental cost-effectiveness		
Societal view point		
Difference in cost per patient		
Difference quality adjusted survival		
Difference in EQ5D QALYs at 6 months		
Incremental cost-effectiveness		

4. Handling uncertainty in cost-effectiveness analysis

   i. Univariate and multi-variate sensitivity analysis (**Table 4) -** One way sensitivity analysis will examine the impact of key variables in the study by varying it across a plausible range of values while holding all other variables constant at their baseline value. Multivariate sensitivity analysis will examine the effect on the results by varying the variables simultaneously across a plausible range.

Table 4: Assumptions to test during sensitivity analysis

	Ranges and thresholds
Type & combination of organ support	Highest & lowest observations
Duration of organ support by type and combination	Highest & lowest observations
Days on ECMO	Highest & lowest observations
Length of stay in Critical Care Unit (ICU & HDU)	Highest & lowest calculated costs
Total length of stay in Hospital	Highest & lowest calculated costs
Cost per day on organ support	Highest & lowest calculated costs
Distance from ECMO centre (cost of transport)	Replacing air with road transport
Change in difference in survival	Upper & lower CI of the attributable benefit

   ii. Confidence interval of ICER - With the availability of patient level data on costs and effects it is possible to summarize uncertainty in the ICER as a confidence interval. The focus here will be to estimate the confidence intervals for ICERs when uncertainty is limited to the NE quadrant of the CE plane (ie when the new treatment under evaluation is both significantly more costly and more effective). Different methods for estimating confidence intervals can give different answers. Therefore, for this study confidence intervals will be calculated by the following methods:

   • The confidence box - The confidence limits are generated and presented on the cost-effectiveness plane and represent the combined confidence intervals for costs and effects (Drummond & McGuire 2001). Combining the 95% confidence limits for costs and effects individually gives a 90% confidence.

   • The confidence ellipse - An improvement over the confidence box. Confidence limits presented as an ellipse. 95% confidence estimates around the point estimate is obtained by this method.

   • Non-parametric bootstrapping - Given the unknown nature of the ICER's sampling distribution, there is reason to be cautious of the parametric approaches to confidence interval estimations. Non-parametric approach of bootstrapping is thought to be a

possible method of estimating confidence intervals. The advantages of such intervals is that they do not depend on parametric assumptions of the sampling distribution of the ICER

5. Cost-effectiveness acceptability curve - Although graphically appealing, the confidence ellipses do not fully address the question of cost-effectiveness, which requires an estimation of the probability of falling within a region of cost-effectiveness. Using bootstrap techniques one can regenerate cost-effectiveness estimates *N* times and generate an acceptability curve. The acceptability curve plots the probability of the new technology being cost-effective based on different valuations of a QALY.

6. Net benefit framework - More recently, the net benefit approach has been introduced to estimate the net benefit of a new treatment programme. The net benefit is the improvement in health multiplied by what we think that improvement is worth (which assumes a social willingness to pay for a QALY), less the additional cost; so net benefit just measures in £s the added benefit of using the new treatment over usual treatment for each patient.

   $NB(\lambda) = \lambda \times \Delta e - \Delta c$

   Sampling distribution of the net benefit statistic can be obtained by bootstrap technique

7. Censored cost data – Censoring occurs whenever study data on patient outcomes collected over time are incomplete. [more will be needed here on the statistical approaches to lost patient data in the trial. At present followup rates are very good, but we are not able to break the randomisation codes to assess whether there is likely to be bias between groups in the rates of loss to followup, other than mortality].

Discounting costs and benefits occurring in the future

The follow-up duration in the trial is 6 months and therefore discounting is not necessary for analysing costs within the trial. However, discounting may become necessary if costs are to be extrapolated to future.

Generalising the results to different settings

It would be beneficial to health care decision makers if economic study results could be generalised from one setting to another as this would avoid having to repeat every study in every setting. Factors which may vary in different settings are: unit costs of resources, geographical variations in demography or epidemiology of disease, clinical practice patterns, incentives to health care professionals and availability of resources.

Effects of some of the above mentioned factors can be limited by proper reporting of results. For example transferability of economic data is made easier if resource use and prices are reported separately and the study population is correctly described and this will be done in reporting of results in this trial.

Additional research planned within the trial

Geographical Information Systems (GIS) modelling study: Initial meetings are in progress to model the location of future beds/ECMO centres if ECMO proves to be cost-effective.

Discussion

Incorporation of economic evaluations within randomised controlled trials of medical therapies has been a growing trend in the past decade. Many health care systems in developed countries now use economic evaluations as a formal input to decisions about whether to fund new technologies. In the UK, economic evaluations play a key role in the technology appraisal process at the National Institute of Clinical Excellence (NICE) which makes decisions about a range of health technologies (NICE 2004).

Economic evaluations conducted alongside randomised trials are meant to inform decision-makers about the economic benefit of the technology under investigation. The information will shed the most light on the question of 'value for money' if the trial and the evaluation are properly designed, if appropriate data are collected and correctly analysed, and if the many sources of uncertainly surrounding these evaluations are adequately addressed. The past decade has seen a large increase in the number of published economic evaluations as well as improvements in economic evaluation techniques. However, much debate and confusion still persist among analysts, readers, and policy-makers concerning methods and the overall usefulness of CEA in resource allocation decision making. A number of potential reasons may account for this, among them political expediency, social preferences and systemic barriers to implementation. In addition, there are a number of more technical shortcomings associated with the generation of economic evidence including methodological inconsistency across completed economic evaluations and the limited generalisability or transferability of findings or settings beyond the location of the original study.

The economic evaluation methodology described in this paper aimed to address these issues and guidelines and recommendations from McGuire and Drummond (2001) were made use of in the design and conduct of the evaluation and the planned analysis. Presenting the methodology paper

before the end of the trial is an attempt to make transparent the methods that are used for the evaluation. This section outlines the strengths and weaknesses of the methodology and points for discussion.

The CESAR Trial was funded with full economic support from the design stages of the trial with funding for three part-time health economists which helped the economic research team to tackle many challenges in the design, methods, data collection, developing and piloting the economic questionnaire and planning the analysis. The trial protocol was developed in collaboration with health economists, who were members of the trial steering group, and an economics working group oversaw the economic evaluation.

The strengths of the trial on which this economic evaluation was based are that it was randomised and controlled, pragmatic in design, and provided a vehicle for collecting a comprehensive set of data on resource use and clinical effectiveness. These provide a reliable basis for estimating the economic efficiency of ECMO for adults with severe respiratory failure. The study cost accounting was comprehensive and included most major health service cost items. Most unit costs used for valuation were from published national sources and where unit costs were unavailable rigorous methods were used for their estimation and the methods used clearly described. Unit costs for ICU stays were estimated for every centre that recruited a patient which was then weighted for each patient to reflect the level of care and number of organs supported during the acute phase of the illness. Very few resource items were excluded from the data collection process alongside the trial. The planned analysis has also incorporated important developments in the analysis and presentation of data.

Points for discussion

- Do the methods described in the paper meet best practice? If not, why not.
- How much research resource is needed for this type of comprehensive work and is it justified? (health economics funding has been 1 wte RA over the length of the trial plus travel)
- Are the methods transparent enough and would this paper be useful for decision makers in the ICU or at national resource allocation advisory bodies.
- At present ECMO is funded only for the trial in the UK by the The National Specialist Commissioning Advisory Group (NSCAG) at the Department of Health. How should this body use trial evidence and should this affect our reporting?
- In the USA, there has been no RCT of ECMO. How could results of the economic evaluation be used there, and should this alter our reporting?

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APPENDIX I

Items of resource use

Sector	Item	Unit cost method
NHS	No of days of Basic respiratory support	HRG study
NHS	No of days of Advanced respiratory support	HRG study
NHS	No of days of Circulatory system support	HRG study
NHS	No of days of Neurological system support	HRG study
NHS	No of days of Renal system support	HRG study
NHS	No of days of Liver system support	HRG study
NHS	No of days on ECMO	HRG study
NHS	No of days on Conventional ventilation	HRG study
NHS	No of days in Intensive care	HRG study
NHS	No of days of other hospital stay before discharge	PSSRU
NHS	No of miles transported by air ambulance	None
NHS	No of miles transported by land ambulance	None
NHS	No of telephone contacts with GP	PSSRU
NHS	No of contacts with NHS direct	PSSRU
NHS	No of visits to GP	PSSRU
NHS	No of contacts with nurse	PSSRU
NHS	Number of contacts with counsellor	PSSRU
NHS	No of contacts with physiotherapist	PSSRU
NHS	No of contacts with occupational therapist	PSSRU
NHS	No of contacts with health visitor	PSSRU
NHS	No of days of inpatient stay	PSSRU
NHS	No of outpatient visits	PSSRU
NHS	Number of A&E visits	PSSRU
NHS	No of visits to day hospital/ day care	PSSRU
NHS	No of days in residential care	PSSRU
NHS	No of days in nursing home	PSSRU
NHS	Types of medication and frequency of use	PSSRU
Social services	No of visits by social worker	PSSRU
Social services	No of visits by homecare worker	PSSRU
Family	No of hours of informal care	Calculated
Family	No of miles of private car use for accessing health care	AA
Family	Out-of-pocket expenses	Reported
Family	Major changes in household	Reported
Family	Childcare costs	Reported
Patient	Change in employment	Reported
Patient	Change in benefits or allowances	Reported
Patient	Loss of income from employment	Reported
Patient	Other costs	Reported
Patient	Other changes	Reported

APPENDIX II

Members of the CESAR Trial Group

1. **Data Monitoring Committee (DMC)** with responsibility for reviewing, in strict confidence, data from the trial approximately half way through the recruitment period and at other intervals if needed.
2. **Steering Committee** with responsibility for monitoring and supervising the trial towards its interim and overall objectives, review relevant information from other sources, consider the recommendations of the DMC, and resolve problems brought by the trial co-ordinating centres
3. **Project Management Group** responsible for the day to day management of the trial.
4. **Data Co-ordinating Group** responsible for co-ordinating data collection, data management, and data analysis
5. **Health Economics group** responsible for designing the economic evaluation of the trial, developing and piloting questionnaires, economic data analysis, and planning and executing unit cost estimation studies.
6. **6-month follow up group** responsible for co-ordinating the follow-up interview at 6 months and health outcomes and resource use data collection at 6 months post-randomisation.

Members of the Health Economics Group

Miranda Mugford, Professor of Health Economics, University of East Anglia, Norwich.
Co-ordinator of the economic evaluation team.

Mariamma Thalanany, Economics Researcher, University of East Anglia, Norwich. Responsible for designing questionnaires, ambulance data collection, designing and carrying out relatives visiting study, planning modelling study.

Clare Hibbert, Research Fellow, ScHARR, University of Sheffield. Responsible for planning and developing ICU costing methodology, related data collection.

Lizzie Coates, Economics Researcher. Working with Clare Hibbert on ICU costing methodology.

Andy Wilson, Senior Lecturer in General Practive, University of Leicester. *R*esponsible for follow-up assessment at six months.

Nicola Cooper, University of Leicester: Key member of modelling study group.

Ann Truesdale, London School of Hygiene and Tropical Medicine (LSHTM): Responsible for co-ordinating data collection and management of trial.

Steve Robertson, LSHTM. Responsible for data management.

Diana Elbourne, Senior statistician, LSHTM: Statistical advice and support

Polly Hardy, Statistician, LSHTM.: Responsible for data analysis, statistical advice and support

Giles Peek, Consultant cardio-thoracic surgeon**,** Glenfield Hospital, Leicester**:** Clinical advice

Ravindranath Tiruvoipati, ECMO Research Fellow, Glenfield Hospital, Leicester. Clinical advice.

Glenfield transport team, Glenfield Hospital, Leicester: Responsible for organising transfer of study subjects between hospitals and ambulance resource use data collection.