Cost-effectiveness of neonatal extracorporeal membrane oxygenation based on 7-year results from the United Kingdom Collaborative ECMO Trial

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared two management strategies, extracorporeal membrane oxygenation (ECMO) and conventional management (CM), aimed at infants with severe respiratory failure.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised mature (gestational age at birth of 35 weeks or more, birth weight of at least 2 kg) newborn infants with severe respiratory failure (oxygenation index >/=40). Infants included in the study were already receiving ventilatory support in accordance with conventional neonatal intensive care unit (NICU) management. The most common diagnoses were persistent pulmonary hypertension due to meconium aspiration, congenital diaphragmatic hernia, isolated persistent foetal circulation, sepsis and idiopathic respiratory distress syndrome. No further inclusion or exclusion criteria were reported.

Setting
The setting was secondary and tertiary care (55 NICUs and 5 specialist regional centres that provided ECMO support). The economic study was carried out in the UK.

Dates to which data relate
Infants were recruited to the study between January 1993 and November 1995. The resource data were collected during the same period. The cost data were derived from sources published between 1998 and 2004, and all costs were reported for the price year 2002/03.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing appears to have been carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations and the method of sample selection were not reported. However, it is likely that these data are reported in the parent clinical study (United Kingdom Collaborative ECMO Trial Group 1996, see ‘Other Publications of Related Interest’ below for bibliographic details). A total of 185 infants were included in the study. Of these, 93 were randomly allocated to the ECMO group and 92 to the CM group.

Study design
The study was a randomised, multi-centre, controlled trial (55 NICUs and 5 specialist regional centres providing ECMO support). The method of randomisation was not reported, but details are given in the parent clinical study (United Kingdom Collaborative ECMO Trial Group 1996). The infants were followed up to 7 years of age (at 1, 4 and 7 years). Ten (5.4%) infants were lost to follow up during the 7-year period. Of these, 2 were lost between initial hospital discharge and 1 year, 4 between 1 and 4 years, and 4 between 4 and 7 years. The reasons for losses to follow-up were not reported, but it is likely that they are given in the parent clinical study (United Kingdom Collaborative ECMO Trial Group 1996).

Analysis of effectiveness
It was not explicitly reported whether the analysis was conducted on an intention to treat basis. The primary health outcomes used were death and long-term morbidity assessed at ages 1 and 4 years. At 7 years (within 3 months of a child's seventh birthday), a developmental psychologist conducted standardised neurodevelopmental assessments. Six clinical areas were assessed (cognitive ability, neuromotor skills, general health, behaviour, hearing and vision) in terms of the degree of functional loss. According to the outcome of the assessment, children were characterised as normal, impaired, or mild, moderate or severely disabled. The overall status was defined according to the highest degree of impairment or disability in any of the six clinical areas. The particular instruments used to evaluate the outcomes and relevant definitions of impairment and functional disability are reported in the parent clinical study (United Kingdom Collaborative ECMO Trial Group 1996).

The characteristics of the two groups were not discussed in the current paper. In addition, it was not reported whether the patient groups were comparable at analysis. Relevant details are provided in the parent clinical study (United Kingdom Collaborative ECMO Trial Group 1996).

Effectiveness results
At 7 years of age the results were as follows.

The number of survivors with severe disability was 3 (3.2%) in the ECMO group and 0 (0%) in the CM group.

The number of survivors with moderate disability was 9 (9.7%) in the ECMO group and 6 (6.5%) in the CM group.

The number of survivors with mild disability was 13 (14.0%) in the ECMO group and 11(12.0%) in the CM group.

The number of survivors with impairment only was 21(22.6%) in the ECMO group and 15 (16.3%) in the CM group.

The number of survivors with no abnormal signs or disability was 10 (10.8%) in the ECMO group and 2 (2.2%) in the CM group.

The number of known survivors with no disability was 31 out of 56 (55.4%) in the ECMO group and 17 out of 34 (50.0%) in the CM group.

It was reported that ECMO was effective in reducing known death or severe disability at 7 years. There were 34 deaths (36.6%) in the ECMO group (n=93) and 54 deaths (58.7%) in the CM group (n=92). The difference in the number of deaths was statistically significant (relative risk 0.64, 95% confidence interval, CI: 0.47 to 0.86; p=0.004).

Clinical conclusions
At 7 years of age, neonatal ECMO was more effective in reducing deaths and increasing the number of survivors free
of disability. However, it resulted in a greater number of survivors with severe disability.

**Measure of benefits used in the economic analysis**
The measures of benefit used were the life-years gained (LYG) and the disability-free LYG. The LYG were estimated by obtaining the date of death from respective health service providers. To estimate disability-free LYG, the authors estimated the period of survival for children whose status was not classified as mild, moderate or severely disabled. In addition, mean net benefits were also estimated for various willingness-to-pay threshold values for an additional life-year and for an additional disability-free life-year.

**Direct costs**
The health service costs included in the analysis were for initial hospitalisation and post-initial hospitalisation.

Initial hospitalisation covered the costs of a day on ECMO (inclusive of drugs, disposables, equipment, staff and overheads), a day on >90% oxygen, a day on a ventilator, supplementary oxygen at any concentration, the daily cost of standard neonatal care and the cost per ambulance journey.

Post-initial hospitalisation covered the costs of inpatient hospital readmission, an outpatient hospital visit (including paediatric visit, surgical visit, cardiology visit, accident and emergency visit, dietician visit, orthoptic visit, neurology visit and audiology visit), visit to a general practitioner, visit of health visitor and visits to other community carers (inclusive of paediatrician, community nurse, physiotherapist, occupational therapist, speech therapist, psychologist, counsellor, ophthalmologist, optometrist and dentist contact hour).

The analysis also included the cost of drugs prescribed by general practitioners and the cost of death (accounting for post-mortem examination and associated procedures, and transport of the deceased infant home by ambulance).

The cost and the quantities of resources used were reported separately in terms of summary costs (e.g. cost of a day on ECMO). The unit costs were based on actual data and were derived from published sources such as the British National Formulary. Where primary research was used to value resource use, the methods adopted were reported. The resource quantities were derived from actual data. Detailed resource use for hospital readmissions, outpatient hospital visits, and the use of community and other health care services was estimated from telephone interviews with the parents (at 4, 8 and 12 months), contacts with general practitioners (at 4 and 7 years), and face-to-face interviews at the child's fourth and seventh birthday. Data obtained directly from the community health service providers were used in a final analysis. It was reported that the unit costs were combined with resource quantities to derive the net cost per child during the trial period. The costs were appropriately discounted and the price year was 2002/03.

**Statistical analysis of costs**
As data on resource items were missing for 18 children, simple linear regression and simulation-based multiple imputation were undertaken for each disability category. The costs were reported as means with standard deviations. Differences in the costs and resources used between the two groups were analysed using independent-sample t-tests, while differences in effects were analysed using the relative risk. Differences were assumed to be statistically significant if two-tailed p-values were \( \leq 0.05 \). Non-parametric bootstrap estimation was employed in the derivation of 95% CIs for mean cost-differences. Because of skewed cost data, 1,000 bias-corrected bootstrap replications were used. In addition, non-parametric bootstrap simulation of the cost-effect pairs was conducted to derive 1,000 replications of each of the incremental cost-effectiveness ratios. This was represented graphically on 4-quadrant cost-effectiveness planes. Mean net benefits and the 95% bootstrap CIs (i.e. defined as the willingness of the English NHS to pay for an additional life-year and for an additional disability-free life-year, multiplied by the difference of incremental effectiveness minus incremental cost) were estimated for different values of willingness-to-pay. Statistical analyses were undertaken using Microsoft Excel and SPSS software.

**Indirect Costs**
The indirect costs were not included in the analysis.
Currency
UK pounds sterling.

Sensitivity analysis
One-way sensitivity analyses were undertaken to investigate the robustness of the results to variability in the data. The parameters investigated were:

- 10%, 20% and 30% increases in community service use, to reflect under-reporting in health economic studies;
- 10% and 20% increases and decreases in the per diem costs of each level of hospital inpatient care, to reflect variability in the relative prices across hospital settings;
- discount rates of 0%, 6% and 10% for future costs and effects, as opposed to 3.5% for the baseline analysis.

A separate analysis was also conducted to estimate the longer term cost-effectiveness of the intervention. The time horizon of the analysis was extended to the first 18 years of life. This analysis was based on three assumptions. First, all children who survive to 7 years will survive to 18 years. Second, the excess annual health service cost due to neonatal ECMO incurred during years 4 to 7 is maintained during years 8 to 18. Finally, each child's disability status at 7 years remains unchanged until 18 years.

Estimated benefits used in the economic analysis
An incremental cost-effectiveness analysis was performed. However, incremental benefits were not reported separately.

Cost results
The mean total health service costs during the first 7 years of life were 30,270 in the ECMO group and 10,299 in the CM group.

The mean cost-difference was 20,041 (bootstrap mean cost-difference 20,057, 95% CI: 13,690 to 26,318). The cost-difference was statistically significant, (p<0.001).

The cost-difference was mainly attributed to increased transportation costs, initial hospitalisation costs and outpatient hospital care in the ECMO group compared with the CM group.

However, it was reported that at a significance level of 5% there were no statistically significant differences in mean cost of inpatient hospital readmissions, community health care and other health services between the two groups.

Synthesis of costs and benefits
The incremental cost per additional LYG was 13,385 (95% CI: 7,967 to 27,672). The incremental cost per additional disability-free LYG was 23,566 (95% CI: 9,751 to 107,632).

The cost-effectiveness acceptability curves demonstrated that, at a willingness-to-pay of 30,000 for an additional life-year, the probability that neonatal ECMO was cost-effective at 7 years was 0.98. Adopting the same willingness-to-pay threshold value for an additional disability-free life-year, it was demonstrated that the probability that neonatal ECMO was cost-effective at 7 years was 0.69.

Sensitivity analyses demonstrated that the results were sensitive to variations in the per diem costs of hospital inpatient care. In particular, when the costs were altered by +/- 20% from baseline estimates, the incremental cost per LYG was increased (and decreased) by 2,303, respectively, and the incremental cost per disability-free LYG was increased and decreased by 4,056, respectively.

The mean net benefits for different willingness-to-pay thresholds were also reported. If a willingness-to-pay value of
10,000 for an additional life-year or an additional disability-free life-year was adopted as a threshold, the mean net benefits to the health service due to neonatal ECMO were -5,299 and -11,387, respectively. In other words, there was a net loss in monetary terms.

When the time horizon of the analysis was extended to 18 years of life, the incremental cost per LYG decreased to 11,802 (95%CI: 5,234 to 56,199). When adopting a willingness-to-pay threshold value of 30,000 for an additional life-year or an additional disability-free life-year, the mean net benefits to the NHS attributed to ECMO were 77,733 and 33,772, respectively, over the time horizon.

Authors’ conclusions
The current study "provides rigorous evidence of the cost-effectiveness of neonatal ECMO (extracorporeal membrane oxygenation) during childhood for mature infants with serve but potentially reversible respiratory failure".

CRD COMMENTARY - Selection of comparators
The comparator was conventional procedures for the management of mature newborn infants with severe respiratory failure. This appears to have represented standard practice in the authors' setting. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a multi-centre, randomised controlled trial, which appears to have been appropriate given the study question. The study referred to newborn infants with severe respiratory failure. However, it was unclear whether the patient groups were comparable at analysis since no details of the patients were provided in the present paper. Although the clinical study appears to have been well conducted, it is not possible to comment on the internal validity of the effectiveness results as the authors referred to a separate clinical paper for details of the clinical study. The effectiveness data were reported comprehensively and were handled credibly in the statistical analyses.

Validity of estimate of measure of benefit
The authors used the LYG and disability-free LYG, as well as monetary net benefits, as measures of benefits in the economic analysis. The benefits appear to have been appropriately estimated. In addition, future benefits were appropriately discounted. The reporting of these benefits offers the opportunity to compare results across different health care programmes.

Validity of estimate of costs
It appears that all the categories of costs relevant to the chosen perspective were included in the analysis. The quantities of resources used and costs were based on primary research in combination with published data. The methodology and the conduct of the research were well reported and should have ensured the quality of the data was adequate. The authors conducted appropriate statistical analyses of the costs and quantities and extensive sensitivity analyses to assess the robustness of the estimates used. The price year and discounting were appropriately reported. These features would facilitate the re-working of the cost data in other settings.

Other issues
The authors compared their findings with those from other studies, at least as far as estimates of resource use and costs were concerned. Differences in the cost estimates were attributed to differing accounting methods. The issue of the generalisability of the results to other settings was directly addressed and enhanced in the sensitivity analyses. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis, as they referred to mature infants with severe, but potentially reversible, respiratory failure.

The authors reported a number of limitations to their study. First, the economic analysis did not incorporate societal costs, the inclusion of which might have resulted in increased costs per additional measure of benefit (i.e. additional
LYG). Second, the authors did not use quality-adjusted life-years as a measure of benefit in the economic analysis, owing to methodological problems and a consequent lack of utility values.

**Implications of the study**
The authors suggested that ECMO offers good value for money within the context of UK decision-making, and that this is a robust finding. Cost-effectiveness also improves over longer time horizons. However, the authors stressed the need for further research. In particular, the evaluation of societal preferences for each health state of the surviving children, the estimation of the cost-effectiveness of neonatal ECMO for different groups of infants, and economic evaluations of different administration methods of neonatal ECMO services. Further research into per diem costs, which were lower than other published data, is also required.

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**Other publications of related interest**
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