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Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants.

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[Intervention Review]

Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Miranda Mugford¹, Diana Elbourne², David Field³

¹School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK. ²Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK. ³University of Leicester, Leicester Royal Infirmary, Leicester, UK

Contact address: Miranda Mugford, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, Norfolk, NR4 7TJ, UK. m.mugford@uea.ac.uk.

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ABSTRACT

Background

Neonatal extracorporeal membrane oxygenation (ECMO) is a complex procedure of life support used in severe but potentially reversible respiratory failure in term infants. Although the number of babies eligible for ECMO is small and the use of ECMO invasive and potentially expensive, its benefits may be high.

Objectives

To determine whether ECMO used for neonatal infants with severe respiratory failure is clinically and cost effective compared to conventional ventilatory support.

Search methods

The Cochrane Neonatal Group Specialised Register, the Cochrane Controlled Trials Register, and MEDLINE were searched for 1974 to 2007.

Selection criteria

All randomised trials comparing neonatal ECMO to conventional ventilatory support.

Data collection and analysis

The authors independently evaluated the trials for methodological quality and appropriateness for inclusion in the Review (without consideration of their results) and independently extracted the data.

Main results

The four trials (three USA and one UK) recruited clinically similar groups of babies. Two trials excluded infants with congenital diaphragmatic hernias. In two trials, transfer for ECMO implied transport over long distances. Two trials had follow-up information. One study included economic evaluation.

The three USA trials had very small numbers of patients. Two trials used conventional randomisation with low potential for bias. Two used less usual designs, which led to difficulties in their interpretation.

All four trials showed strong benefit of ECMO on mortality (typical RR 0.44; 95% CI 0.31 to 0.61), especially for babies without congenital diaphragmatic hernia (typical RR 0.33, 95% CI 0.21 to 0.53).

The UK trial provided follow up information about death or severe disability, and cost-effectiveness, and showed benefit of ECMO at one year (RR 0.56, 95% CI 0.40 to 0.78), four years (RR 0.62, 95% CI 0.45 to 0.86), and seven years (RR 0.64, 95% CI 0.47 to 0.86). Overall nearly half of the children recruited had died or were severely disabled by seven years of age, reflecting the severity of their underlying conditions. A policy of ECMO is as cost-effective as other intensive care technologies in common use.

Authors' conclusions

A policy of using ECMO in mature infants with severe but potentially reversible respiratory failure results in significantly improved survival without increased risk of severe disability. The benefit of ECMO for babies with diaphragmatic hernia is unclear.

Further studies are needed to consider the optimal timing for introducing ECMO; to identify which infants are most likely to benefit; and to address the implications of neonatal ECMO during later childhood and adult life.

PLAIN LANGUAGE SUMMARY

Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

A complex life support procedure, called extracorporeal membrane oxygenation (ECMO), can be used in infants who are near term age to overcome severe, potentially reversible breathing problems. ECMO is similar to the technology used in cardiac bypass surgery. Blood is removed from the body of the patient, oxygen is added to the blood, and the blood is returned to the patient. Although the number of babies requiring ECMO is small, and ECMO is a very invasive and potentially expensive procedure, the benefits of this procedure are high. In this review, four randomized trials that compared the use of ECMO to the conventional approach to supporting these infants with severe breathing problems were identified. Overall, these trials showed a strong benefit for ECMO regarding survival at the time of hospital discharge. This is particularly true for infants without a specific problem of lung formation (congenital diaphragmatic hernia). The result implies that for every three babies with breathing problems and lung failure who were treated with ECMO rather than conventional ventilation, one more infant will survive. Although little information is available regarding long-term follow-up, one trial in the United Kingdom shows both benefits of ECMO and cost-effectiveness of the use of ECMO.

BACKGROUND

Extracorporeal membrane oxygenation (ECMO) is a complex technique for providing life support in severe but potentially reversible respiratory failure. The technique oxygenates blood outside the body, obviating the need for gas exchange in the lungs and, if necessary, provides cardiovascular support. It is most commonly used to support mature newborn infants, as preterm infants are not suitable both because of the size of the cannulae required, and because of their additional risk of intraventricular haemorrhage associated with the use of heparin.

The concept arose as an off-shoot of cardiopulmonary by-pass technology. Initially it was used to support adults, but early results were poor. Similarly, early attempts to use ECMO in the treatment of newborns were unsuccessful; cannula problems provided the greatest technical difficulty. However, in 1975 Bartlett reported the first mature newborn treated successfully with ECMO

and other reports soon followed (Bartlett 1976). It subsequently became clear that mature infants with persistent pulmonary hypertension of the newborn (PPHN) were particularly suited to ECMO, since the better oxygenation and physiological stability produced by ECMO improved pulmonary blood flow without the risk of further barotrauma.

ECMO is an extremely invasive and technically involved procedure. Traditional ECMO uses two large gauge catheters, one placed in a central vein and the other in a central artery (venoarterial or V-A). It is essential to achieve adequate flow rates (approximately 100 - 120 ml/kg/min) and as a result cannulae are normally 12 - 14 French gauge. Blood is drained passively via the venous catheter which is inserted into the internal jugular vein and positioned in the right atrium. Blood then passes on to a pump which maintains flow in the circuit. A 'bladder box' and servo system prevent the pump from working if venous drainage

becomes inadequate for any reason. Blood then passes to an oxygenator where a sweep gas passes in counter current to the blood. The concentration of oxygen in the sweep gas can be adjusted depending on the needs of the patient. Before re-entering the body, warming occurs in a heat exchange column. Blood is returned via the common carotid artery at systemic pressure. This type of ECMO is able to support both pulmonary and cardiac function. More recently, veno-venous (V-V) ECMO, which provides just pulmonary support, has become popular and is now used increasingly. The particular, theoretical, advantage of V-V ECMO is that the cerebral arterial blood supply is not disrupted.

While on ECMO additional gas exchange by the lungs is not essential and therefore ventilation is normally reduced to 'rest' settings. This is typically 5 - 10 cm H₂O positive end expiratory pressure and 10 to 20 breaths per minute but the exact approach does vary from centre to centre. This strategy prevents any further lung damage secondary to barotrauma but arrests the atelectasis, which might follow acute withdrawal of respiratory support and enhances clearance of secretions.

The point in an individual baby's course at which ECMO should be considered is debatable. A variety of physiological and clinical parameters have been used. Over time, oxygenation index (OI) of greater than 40 has probably become the most widely employed, where

$$OI = (FiO_2) * (\text{mean airway pressure cm H}_2\text{O}) * 100 / PaO_2 \text{ mm Hg.}$$

Although the absolute number of babies who reach this level of severity is never likely to be large, the potential benefits of ECMO may be extremely high. However, ECMO is very invasive and because it is so labour intensive, it is expensive. Hence there is a need for rigorous evaluation of its advantages and disadvantages to guide practice.

OBJECTIVES

To determine whether ECMO used for neonatal infants with severe respiratory failure is clinically effective (especially in terms of mortality and childhood disability) compared to a policy of conventional ventilatory support. The two approaches will also be assessed in terms of their relative resource use and cost-effectiveness.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing neonatal ECMO to conventional ventilatory support

Types of participants

All infants with severe but potentially reversible respiratory failure, aged less than 28 days, with gestation at birth of 34 weeks or more were included. Trials relying on a range of physiological parameters to identify infants who had "severe but potentially reversible respiratory failure" (e.g. PaO₂ < 40 mm Hg or pH < 7.15 for two hours) as well as those using the criterion of an oxygenation index of > 40 to select patients were all included.

Secondary analyses of the primary outcomes (see below) are based on those with and without a primary diagnosis of congenital diaphragmatic hernia, and by severity (oxygenation index between 40 to 60, and over 60)

Types of interventions

Extracorporeal membrane oxygenation versus conventional ventilatory management

Types of outcome measures

Outcome measures focused on mortality, disability and use of health service resources. Specifically, the primary outcomes are death, death or severe disability, death or disability, severe disability, and any disability, all considered at discharge from hospital, at one year, at four years, at seven years, and to the end of data collection.

Other outcomes include impairment (with or without disability) at one year of age, readmission to hospital in the first year, need for supplemental oxygen at one year of age, tube feeding at one year, weight < the 3rd percentile at one year of age, head circumference < the 3rd percentile at one year of age, head circumference > the 97th percentile at one year of age, visual problems at one year of age, hearing problems at one year of age, on anticonvulsants at one year of age, changes in neuromotor tone at one year of age, asymmetrical neuromotor signs at one year of age, abnormal axial tone at one year of age, abnormal movements at one year of age, motor developmental quotient < 50 at one year of age, motor developmental quotient < 70 at one year of age, overall developmental quotient < 70 at one year of age, professional support for special needs at four years of age. Other outcomes at seven year include information on any disability and severe disability in the cognitive, neuromotor, general health, behaviour, visual and hearing domains.

Outcomes indicating use of resources indicating levels of intensiveness, and therefore cost, of care are: days on ECMO, days on oxygen > 90%, days on ventilator, days on supplemental oxygen before first discharge home, and days in hospital before first discharge home. These categories are not mutually exclusive. Further indication of increased or reduced health and other care resource

use is given by the readmission to hospital one year of age; professional support for special needs up to four years; and days in hospital, outpatient hospital visits, and visits by family doctors, health visitor and other professionals, up to seven years. Incremental cost per additional survivor and per additional survivor without disability at one, four and seven years of age are also reported in local currency values, without summary statistics. Other outcomes not considered in the review protocol but provided by authors have been given within the Included Studies Table.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2007) and the Cochrane Neonatal Group Specialised Register were searched using keywords ECMO, extra corporeal membrane oxygenation, extracorporeal membrane oxygenation, extra-corporeal membrane oxygenation, and neonat*. MEDLINE was also searched. Searches covered the period 1974 to 2007.

Data collection and analysis

Trials under consideration were evaluated for their methodological quality (in terms of concealment of allocation, masking of intervention (where appropriate), completeness of follow-up, and masking of outcome assessment (where appropriate)), and appropriateness for inclusion in the review, by two authors independently, without consideration of their results.

Trial data were extracted by two authors independently

Further information was sought from the authors of the trials, as appropriate.

Analysis was by intention to treat, using Review Manager (RevMan) software. For dichotomous data, summary relative risks were calculated using a fixed effects model providing there was no significant heterogeneity. For continuous data, weighted mean differences were calculated. 95% confidence intervals were used. Trials that included economic analysis were noted, and associated publication of economic findings referenced. Critical abstracts of economic evaluations of ECMO are available in the NHS economic evaluation database, which is also included in the Cochrane Library. In this review, data about key items of resource use and patient based costs are reported. Where studies meet BMJ criteria for economic evaluation (Drummond 1996) and also report measures of incremental cost-effectiveness, this is also reported.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The original review identified four trials, all of which met the entry criteria. No further trials were identified in 2006 search but four new papers were considered. One paper (Schaub 2002) was the report in German of the UK ECMO trial (see below). Three other papers were reports of the follow-up from the UK ECMO trial, including the seven year follow-up (McNally 2006) and two economic evaluations - at four years (Petrou 2004), and at seven years (Petrou 2006).

Three of the four trials were carried out in the USA (Boston 1989; Michigan 1985; and Syracuse 1992), and one in the UK (UK 1996). All four trials recruited clinically similar groups of term or near-term newborn babies with severe respiratory distress, although two (Boston, Syracuse) excluded infants with congenital diaphragmatic hernias. In two of the trials (Syracuse 1992; and UK 1996), transfer for ECMO usually implied transport over a considerable distance, whereas in Michigan all the babies were cared for in the same hospital, and in Boston the ECMO centre was in the same city.

One study was associated with a full economic evaluation, reported separately (Roberts 1998; Petrou 2004; Petrou 2006). The related economic studies meet criteria for inclusion in the NHS Economic Evaluation Database (NHSEED). The first report of the economic evaluation of the UK trial (Roberts 1998) is updated by Petrou 2006. Hyperlinks for the NHSEED critical abstracts of these papers are:

<http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=21998008232> (Roberts 1998)

<http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=22004000682> (Petrou 2004).

<http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=22006006380> (Petrou 2006)

Risk of bias in included studies

Data from the Syracuse trial have only been published as two conference abstracts. Although the investigators kindly provided copies of the slides which they used at the respective conferences and updated the information on the Bayley scores, the data were not always sufficient to be able to fully assess the methodological quality of the trial.

All the trials except the UK trial had very small numbers of patients. Three of the trials (Boston, Michigan and UK) were stopped early for effectiveness on the advice of the relevant Data Monitoring Committee, in accordance with pre-specified stopping rules in their trial protocols. Nevertheless, as early stopping is often associated with a random high, it is possible that the reported effect sizes may be exaggerations of the true treatment effect.

Two of the trials (Syracuse and UK) used conventional randomi-

sation methods with low potential for selection bias at trial entry. They also used an intention to treat analysis based on patients in the groups to which they were randomised, and with virtually no loss to follow-up. Although the treatments could not be masked after randomisation, the outcome measures such as death were unlikely to be subject to observer bias, and the assessors at paediatric follow-up in the UK trial were kept unaware of the treatment allocation.

There were more problems about methodological quality in the other two trials which used less usual designs. Both employed a Zelen design (Zelen 1979) in which informed consent to treatment was requested after randomisation and only in the ECMO arm. This method has high potential for selection biases before and after trial entry if the recruiting clinician, on seeing which treatment has been randomly allocated to a particular patient, then does not ask that patient /parent for consent to the (known) treatment and/or to the follow-up; parents may also decide not to consent to a particular treatment, and/or to enter their baby into the trial and/or to give permission for follow-up. The potential for bias arises because these decisions are made in knowledge of the allocated treatment and may therefore be differentially affected by that knowledge. This may be even more of a problem if, as in these ECMO trials, a single consent design is used, as one group may not have the opportunity to refuse. The trial reports do not provide sufficient information to be able to assess the extent of these biases (although the Boston trial states that there were no post-randomisation exclusions).

They also used 'response-adaptive' designs. In the Boston trial, this led to a decision to halt randomisation after the fourth death in either trial group. (There was also subsequently a non-randomised phase of this trial, but data from that phase have not been used in this review). In the Michigan trial, the adaptive design used the 'play the winner' strategy in which the first patient was given an equal chance of randomisation to either trial arm, but subsequent allocations were based on the results for the previous allocation, with a higher probability of allocation to the treatment doing better at the time. This has led to a major imbalance in the numbers of infants in each trial arm (only one in the conventional management arm). These unusual designs have led to difficulties in the interpretation of their results.

All four studies reported one or more of the defined resource use outcomes, but the three American studies provided this information for survivors only. The economic evaluations reported from the UK study are from the health services viewpoint, taking account of both hospital and community care costs. The resource use cost analysis is most relevant to the UK NHS, where the economic analysis was conducted. Full economic analyses of cost effectiveness were conducted at one, four and seven years, and sensitivity and uncertainty analysis was also included.

Effects of interventions

Very few of the trials provided information about all the planned outcomes, and only the UK and Syracuse trials had any follow-up information. Therefore, very few of the comparisons show data for all the outcomes, either overall, or in the pre-specified subgroups.

Mortality

Death before discharge home (or to the end of data collection) were the only outcomes reported for all four trials. For death before discharge home, each of the four trials showed a strong benefit of ECMO, but as the three US trials were all very small, the size of effect (typical RR 0.44) was overwhelmingly determined by the UK trial and the 95% CI was very tight (0.31 to 0.61), a highly statistically significant benefit ($p < 0.00001$) (Outcome 1.1). This can also be expressed as a difference in rates of -0.32 (95% CI -0.44 to -0.20), implying only three babies need to be treated with ECMO rather than conventional ventilation to prevent one death. The situation was similar for deaths to the end of data collection (typical RR 0.51, 95% CI 0.37 to 0.70; $p = 0.00003$) (Outcome 1.3), although there were some later deaths in the ECMO arm (from the trials with follow up).

The majority of patients in these trials did not have congenital diaphragmatic hernia as the primary diagnosis either because this was an exclusion criterion (Boston and Syracuse) or because the numbers with this primary diagnosis were relatively small (1/12 in the Michigan trial and 35/185 in the UK trial). The risk of death by discharge for babies without this diagnosis was reduced even more (typical RR 0.33, 95% CI 0.21 to 0.53; $p < 0.00001$) (Outcome 2.1). The results were similar for deaths to the end of data collection (typical RR 0.41, 95% CI 0.27 to 0.63; $p = 0.00004$) (Outcome 2.3). Even for the 35 babies in the UK trial with a primary diagnosis of congenital diaphragmatic hernia, the risk of death at four years was reduced (RR 0.84, 95% CI 0.67 to 1.05; $p = 0.08$) but only five infants survived to discharge, and only three children survived to seven years of age, all in the ECMO arm (17/17 of the infants in the conventional management arm died before discharge).

Death or disability

Only the UK trial provided information about death or disability at one, four and seven years. This again showed an overall benefit of ECMO at one year (RR 0.56, 95% CI 0.40 to 0.78; $p = 0.006$) (Outcome 1.7), and at four, and seven years (RR 0.62, 95% CI 0.45 to 0.86; $p = 0.004$) (Outcomes 1.26, 1.28). The benefit was even more marked in the subgroup of children who did not have a primary diagnosis of congenital diaphragmatic hernia at trial entry (RR at one year 0.45, 95% CI 0.28 to 0.72; $p = 0.009$), and at four and seven years (RR 0.49, 95% CI 0.31 to 0.77; $p = 0.002$). The trend towards benefit for the children with congenital diaphragmatic hernia at trial entry was much less marked (RR at one year 0.78, 95% CI 0.61 to 1.00; $p = 0.05$) (Outcome 2.6), and at four years (RR 0.89, 95% CI 0.75 to 1.05; $p = 0.16$) (Outcome 2.7), with only two children alive and not severely disabled, both in the ECMO arm.

The Oxygenation Index at trial entry was used as a measure of

severity. The effect of a policy of ECMO by four years of age was more marked in the less severe stratum of OI 40 - 60 (death or severe disability at four years RR 0.52, 95% CI 0.31 to 0.85; $p = 0.010$) than the more severe stratum of OI > 60 (death or severe disability at four years RR 0.76, 95% CI 0.52 to 1.12; $p = 0.16$) although the trend is in the same direction.

Disability and impairment

Data from the UK trial at one year showed no clear trend in relation to the risk of disability or impairment. Assessment of children at one year is difficult to interpret and hence developmental assessments are likely to have lacked precision.

At four years much more detailed information was available. Five children were lost to follow-up (three in the conventional management group). Of the 60 randomised to ECMO and assessed at four years, 12 appeared normal and 18 had signs of impairment without disability. The remaining 30 had signs of disability (three severe). In the conventional arm 35 children were assessed, of whom four appeared normal with nine having signs of impairment without disability. The other 22 children in this group were disabled but none were considered severe. The data did not suggest that an increased risk of particular types of adverse neurodevelopmental outcome (e.g. hemiplegia) was associated with either group.

Four children were lost to follow-up between the ages of four and seven. By seven years, extra information was available, particularly about cognition and behaviour.

Of the 56 randomised to ECMO and assessed at seven years, 10 appeared normal and 21 had signs of impairment without disability. The remaining 25 had signs of disability (three severe). In the conventional arm 34 children were assessed, of whom two appeared normal with 15 having signs of impairment without disability. The other 17 children in this group were disabled but none were considered severe.

Use of health services

Measures of resource use were analysed as continuous variables. In the initial hospitalisation, more resources were used in the ECMO arm, including ECMO days, days on ventilator, days on supplementary oxygen, days of standard neonatal care, days in hospital and transport. The only exception was in the case of days on more than 90% oxygen, where conventionally managed babies had a mean of 3.56 days compared to 1.48 days for the ECMO arm. Differences in resource use at this stage are partly explained by higher early mortality in the conventional management arm.

In the period from discharge from initial hospitalisation until seven year follow-up, there was consistently higher use of health care resources in the ECMO arm, but this is largely because of increased survival in this group.

Costs and cost effectiveness

The incremental cost effectiveness ratio (ICER) of ECMO over seven years was estimated to be £13,385 (95%CI 7,967 to 27,672) per life year gained, and to be £23,566 (95% CI 9,571 to 107,632) per disability free life year gained. The sensitivity analysis for cost

effectiveness in subgroups showed that for children diagnosed with no diaphragmatic hernia, the incremental cost effectiveness per life year gained was £8,082, and per disability free life year gained, £14,124. The equivalent ICERs for children with diaphragmatic hernia were £42,080 and £79,013. The purchasing power parity between £GB to US\$ in 2003 was £0.627 GB=\$1US (OECD 2006).

DISCUSSION

There was clear benefit for the ECMO policy in terms of reducing mortality and, although there were some later deaths in the ECMO arm, the balance of benefits remains strongly in favour of the ECMO policy for this outcome. Although there was a non-statistically significant tendency towards more disability in the ECMO group at one year, this was no longer the case by four or seven years of age in the UK trial. There was also an important benefit of ECMO when considering the composite outcome of death OR severe disability at one, four and seven years of age. Fuller details of other outcomes from the UK trial shown in the accompanying figures do not alter these conclusions, although numbers of children with any one specific adverse outcome are small.

The diagnosis of severe but potentially reversible respiratory failure is not straightforward. Over the time that ECMO has been available a variety of indices have been used in this role. All are intended to identify babies with a high probability of death from continued conventional therapy. The results of this review would indicate that they achieve this aim. The various measures used to identify suitable infants have not been compared but this seems unnecessary given the randomised nature of the subsequent studies.

The invasive nature of ECMO has been the cause of much concern. The potential for acute problems related to the ECMO circuit and the inevitable disruption to the cerebral circulation led many to make the broad assumption that there was an inherent risk attached to the use of ECMO which would inevitably result in increased morbidity. These concerns have not been born out. Since the risks are undeniable it would appear that the damaging effect of prolonged exposure to aggressive conventional therapy as used in the 1990s are even greater. It is important to note that only a minority of all recruited infants could be considered normal survivors at seven years. Although ECMO has been considered as a single entity in this comparison there was significant use of the veno venous technique in the UK study whilst this was not the case in earlier trials.

The majority of patients in these trials did not have congenital diaphragmatic hernia as the primary diagnosis either because this was an exclusion criterion (Boston and Syracuse) or because the numbers with this primary diagnosis were small (1/12 in the

Michigan trial and 35/185 in the UK trial). Although the balance of benefit was still marginally in favour of the ECMO policy (17/17 of the infants in the conventional management arm died before discharge), by the age of seven years, 16/18 of those in the ECMO arm had also died or were severely disabled.

There was no evidence that the severity of illness as judged by an OI of 40 to 60 or over 60 affected the benefit of the ECMO policy.

Although there is a clear benefit for the ECMO policy, overall nearly half of the children had died or were severely disabled at four years of age, reflecting the severity of their underlying conditions. Nevertheless, based on the economic analysis from the UK trial, the ECMO policy is not only clinically effective but also as cost-effective as other intensive care technologies in common use.

AUTHORS' CONCLUSIONS

Implications for practice

A policy of using ECMO in mature infants with severe but potentially reversible respiratory failure would result in significantly improved survival without any increased risk of severe disability amongst survivors. A variety of indices can be used to define such infants but the use of an oxygenation index of 40 seems the most straightforward.

The situation for babies with diaphragmatic hernia is less clear since, despite their common underlying anomaly, they do not represent a homogeneous group. It would appear that ECMO offers short term benefits but the overall effect of employing ECMO in this group is not clear. In the absence of a definitive study the use of ECMO can only be recommended on clinical grounds i.e. where it can be used to stabilise a baby thought to be potentially viable but failing more conventional support.

Cost effectiveness is sensitive to the organisation of health care for ECMO and intensive neonatal care. Lower cot occupancy and higher staff to cot ratios increase costs, as do long travel times and distances.

Implications for research

Further studies are needed to refine ECMO techniques in an attempt to reduce both short term risks (such as circuit failure) and the damage that might result from physiological disruption. A formal comparison of veno venous and veno arterial ECMO seems particularly important in this regard.

The identification of suitable infants also merits further consideration. At present infants are referred for ECMO when other therapies have failed and the baby is continuing to deteriorate. Outcomes might be improved by introducing ECMO earlier, i.e. as soon as all other therapies have failed.

The longer term effects of neonatal ECMO (e.g. during later childhood, adolescence and adult life) remain unclear. Studies to address these issues are clearly important if infants are going to continue to be offered this form of life support.

The correct approach to the management of infants with diaphragmatic hernia is not known. Large randomised studies, with long term follow-up, are needed in order to establish both the best approach to acute management and the extent to which "normal survival" is achievable with our present treatment options. There is some uncertainty about what constitutes "present treatment options" and establishing the test arms would clearly be the first step in developing such a study.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Boston 1989

Methods	Adaptive design with single consent Zelen randomisation. No post- randomisation exclusions. Randomisation in balanced blocks of size 4 and planned to cease after 4th death in either group. Phase II was non-randomised enrolment in group with <4 deaths until 4th death in that group or number of survivors significantly larger than number of survivors in arm discontinued first
Participants	19 infants with severe persistent pulmonary hypertension and respiratory failure. Birthweight \geq 2.5 kg, gestational age \geq 38 weeks, normal cranial ultrasound, severe hypoxemia, 80% predicted mortality based on $\text{PaO}_2/\text{PAO}_2 \leq 0.15$ on 2 occasions > 30 mins apart between 12 and 72 hours after birth. Exclusions: congenital diaphragmatic hernia, heart disease
Interventions	Extra Corporeal Membrane Oxygenation (venoarterial) usually involving transport to a multidisciplinary intensive care unit (within Boston). Conventional treatment remained on optimal ventilatory support in initial neonatal intensive care unit
Outcomes	Death, duration of ventilation and of supplemental oxygen, intracranial haemorrhage, complications of ECMO
Notes	Methodological quality Masking of intervention (not possible) Completeness of follow-up (yes, until discharge) Masking of outcome assessment (mortality outcome so masking not appropriate)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Michigan 1985

Methods	Adaptive design with single consent Zelen randomisation. 'Play the winner' - 1st patient equal chance of randomisation to either arm, but subsequent assignments based on results for previous patients - higher probability for treatment doing better
Participants	12 infants with newborn respiratory failure; > 2kg birthweight; any of following: 1 acute deterioration $\text{PaO}_2 < 40$ mmHg of $\text{pH} < 7.15$ for 2 hours 2. Unresponsiveness (2 of 3 indication for 3 hours - $\text{PaO}_2 < 55$, $\text{pH} < 7.4$ or hypotension 3. barotrauma 4. congenital diaphragmatic hernia 5 80%+ mortality index at 24 hours Exclusions: intracranial haemorrhage grade II or more; > 7 days; incompatible with normal quality life

Michigan 1985 (Continued)

Interventions	Single centre for both treatments. Extra Corporeal Membrane Oxygenation (venoarterial if signs of haemodynamic instability, otherwise veno-venous). Conventional treatment remained on optimal ventilatory support	
Outcomes	Death, duration of ventilation and of hospital stay, intracranial haemorrhage, complications of ECMO some follow up	
Notes	Methodological quality Masking of intervention (not possible) Completeness of follow-up (yes, until discharge) Masking of outcome assessment (mortality outcome so masking not appropriate)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Syracuse 1992

Methods	Assigned randomly (no other details).	
Participants	28 infants with respiratory failure - oxygenation index >40 for 4 hours; >35 weeks; >= 2 kg; 10 days; Exclusions: intraventricular haemorrhage, structural heart disease, congenital diaphragmatic hernia; severe congenital anomaly	
Interventions	Single centre for conventional treatment. Transport for Extra Corporeal Membrane Oxygenation (venoarterial) in one of 3 centres. Conventional treatment remained on optimal ventilatory support	
Outcomes	Death, duration of ventilation, of supplemental oxygen, and of hospital stay, intracranial haemorrhage, complications of ECMO. Follow up to 2 years - neurological abnormality, Bayley scores	
Notes	Methodological quality Masking of intervention (not possible) Completeness of follow-up (yes, until discharge, and good at follow up) Masking of outcome assessment (masking not appropriate for mortality outcome; not clear if paediatric assessor masked)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

UK 1996

Methods	Central telephone randomisation with minimisation on primary diagnosis, severity, and referral hospital and ECMO centre
Participants	185 infants with severe respiratory failure (oxygenation index >40); > 2kg birthweight; >35 weeks gestation; <10 days high pressure ventilation; < 28 days old; no contraindication for ECMO (ventricular haemorrhage, irreversible cardiopulmonary disease, asystole, necrotising enterocolitis); no major congenital anomaly
Interventions	Transport for Extra Corporeal Membrane Oxygenation (venoarterial) in one of 5 centres. Conventional care in centre accustomed to providing optimal ventilatory support
Outcomes	Death, duration of ventilation, of supplemental oxygen, and of hospital stay, intracranial haemorrhage, complications of ECMO. Follow up to 1 and 4 years - respiratory, growth, vision, hearing, neuromotor/neurological abnormality, Griffith scores; disability and impairment; health service use and cost effectiveness. Follow-up at 7 years, - assessments of respiratory, growth, vision, hearing, neuromotor/neurological abnormality, disability and impairment, cognition (British Ability Scales), memory and behaviour, health service use and cost effectiveness
Notes	Methodological quality Masking of intervention (not possible) Completeness of follow-up (yes, until discharge, and good at follow-up) Masking of outcome assessment (masking not appropriate for mortality outcome, and paediatric assessment was masked)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Schaub 2002	This is just a report in German of the UK ECMO trial

DATA AND ANALYSES

Comparison 1. All eligible infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death before discharge home	4	244	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.31, 0.61]
2 Death in the first year of life	2	213	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.37, 0.73]
3 Death at any time to the end of data collection	4	244	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.37, 0.70]
4 Severe disability in survivors at one year of age	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.04, 9.26]
5 Disability (severe and not severe) in survivors at one year of age	2	119	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.62, 3.51]
6 Impairment (with or without disability) in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Death or severe disability at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Readmission to hospital in survivors in first year	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.46, 1.01]
9 On supplemental oxygen in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Tube feeding in survivors at one year	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Weight < 3rd centile in survivors at one year of age	2	119	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.52, 6.20]
12 Head circumference < 3rd centile in survivors at one year of age	2	119	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.53, 16.11]
13 Head circumference > 97th in survivors centile at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Vision problems in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15 Hearing problems in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16 On anticonvulsants in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17 Neuromotor tone changes in survivors at one year	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18 Asymmetrical neuromotor signs in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19 Abnormal axial tone in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20 Abnormal movements in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

21	Motor Developmental Quotient less than 50 in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
22	Motor Developmental Quotient less than 70 in survivors at one year of age	2	119	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.43, 3.93]
23	Overall Developmental Quotient less than 70 in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
24	Severe disability in survivors at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
25	Any disability in survivors at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
26	Death or severe disability at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
27	Professional support for special needs in survivors at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
28	Death or severe disability at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
29	Death by 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
30	Severe disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
31	Any disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
32	Any cognitive disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
33	Severe cognitive disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
34	Any neuromotor disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
35	Severe neuromotor disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
36	Any general health disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
37	Severe general health disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
38	Any behavioural disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
39	Severe behavioural disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
40	Any visual disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
41	Severe visual disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
42	Any hearing disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
43	Severe hearing disability in survivors at 7 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
44	Days on ECMO	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
45	Days on > 90% oxygen	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

46 Days on ventilator	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
47 Days on supplementary oxygen at any concentration	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
48 Days on standard neonatal care	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
49 Days in hospital (initial admission)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
50 Number of ambulance journeys	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
51 Days in hospital (all re-admissions up to 7 years)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
52 Number of hospital outpatient visits up to 7 years	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
53 Number of family doctor visits up to 7 years	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
54 Number of health visitor visits up to 7 years	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
55 Number of visits by other professionals up to 7 years	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
56 Total health service costs (£GB 2003 prices)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death before discharge home	4	208	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.21, 0.53]
2 Death in the first year of life	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.28, 0.68]
3 Death at any time to the end of data collection	4	208	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.27, 0.63]
4 Severe disability in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Disability (severe and not severe) in survivors at one year of age	2	115	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.07]
6 Death or severe disability at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Death or severe disability at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Infants with congenital diaphragmatic hernia as principal diagnosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death before discharge home	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Death in the first year of life	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death at any time to the end of data collection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Death or severe disability at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Death or severe disability at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Infants with oxygenation index 40-60 at trial entry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe disability in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Disability (severe and not severe) in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death or severe disability at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Infants with oxygenation index > 60 at trial entry

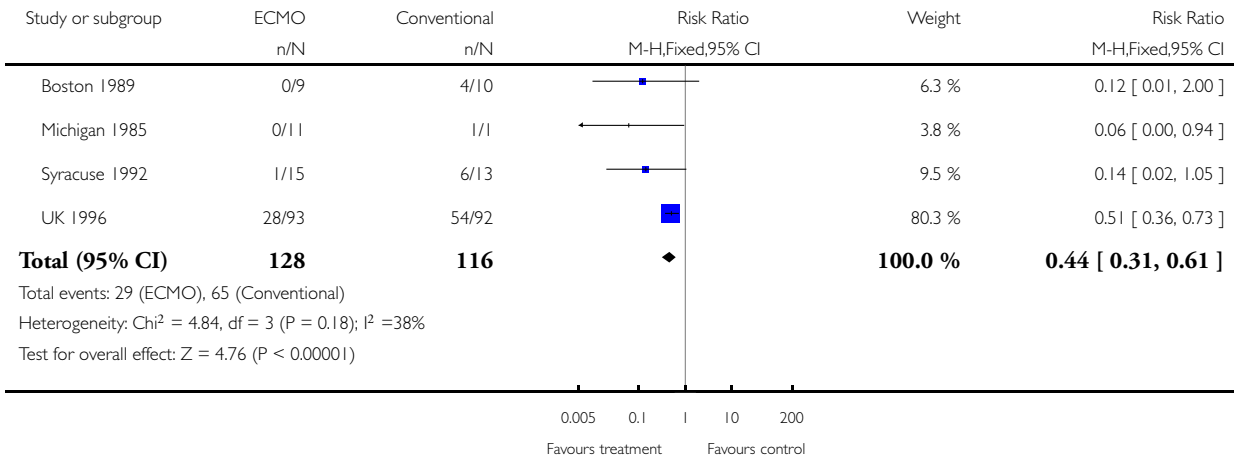
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe disability in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Disability (severe and not severe) in survivors at one year of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death or severe disability at 4 years of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 All eligible infants, Outcome 1 Death before discharge home.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 1 Death before discharge home

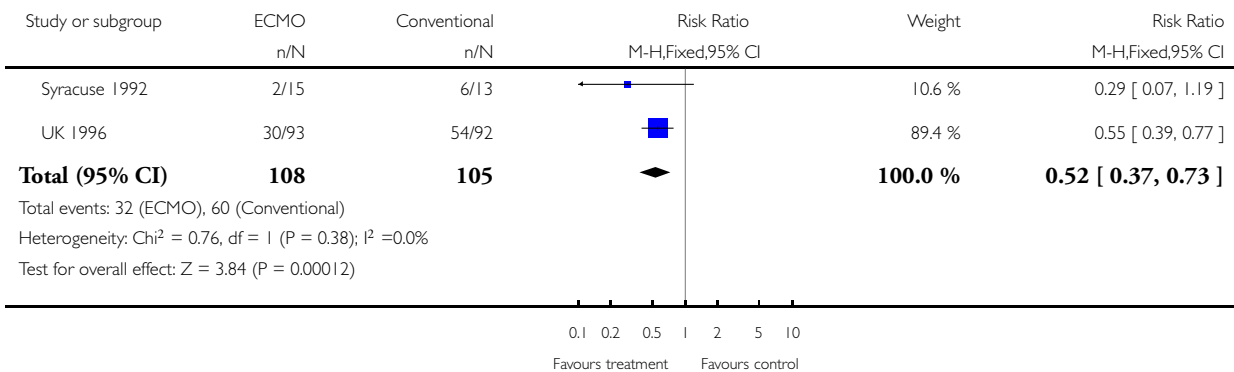


Analysis 1.2. Comparison 1 All eligible infants, Outcome 2 Death in the first year of life.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 2 Death in the first year of life

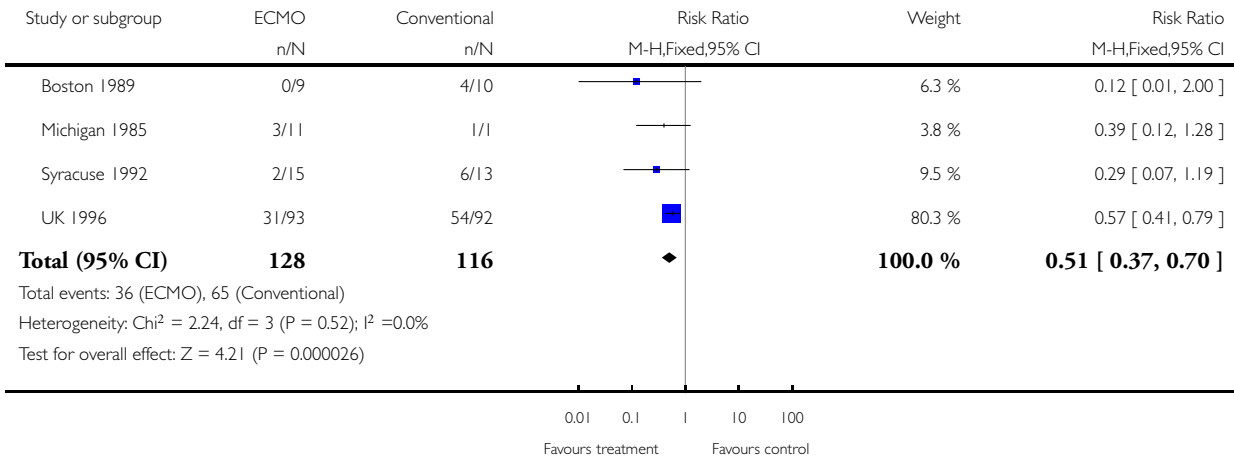


Analysis 1.3. Comparison 1 All eligible infants, Outcome 3 Death at any time to the end of data collection.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 3 Death at any time to the end of data collection

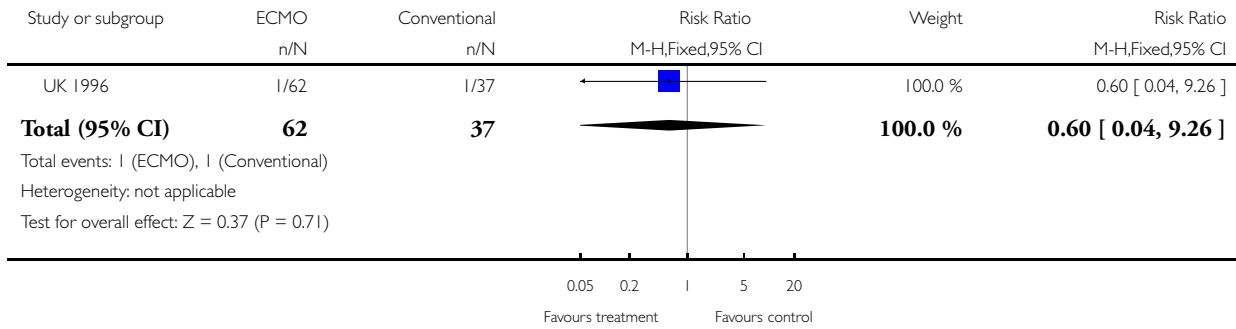


Analysis 1.4. Comparison 1 All eligible infants, Outcome 4 Severe disability in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 4 Severe disability in survivors at one year of age

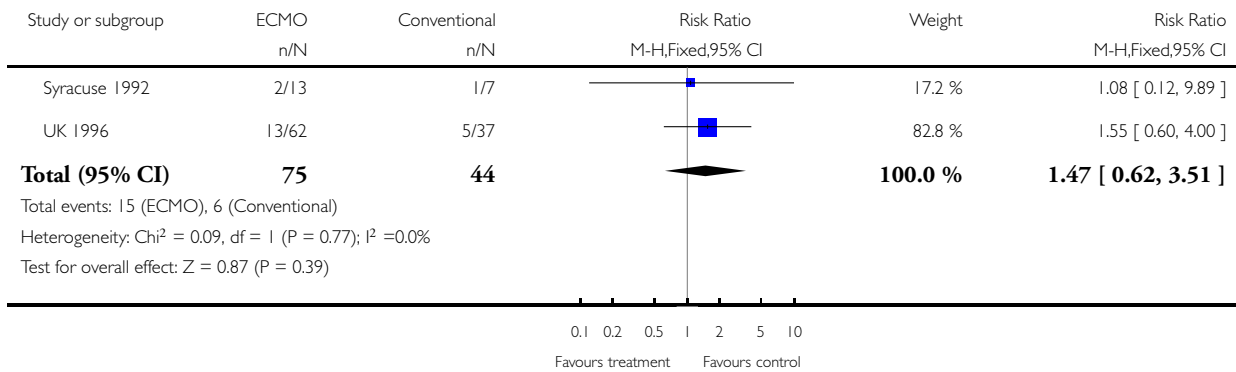


Analysis 1.5. Comparison 1 All eligible infants, Outcome 5 Disability (severe and not severe) in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 5 Disability (severe and not severe) in survivors at one year of age

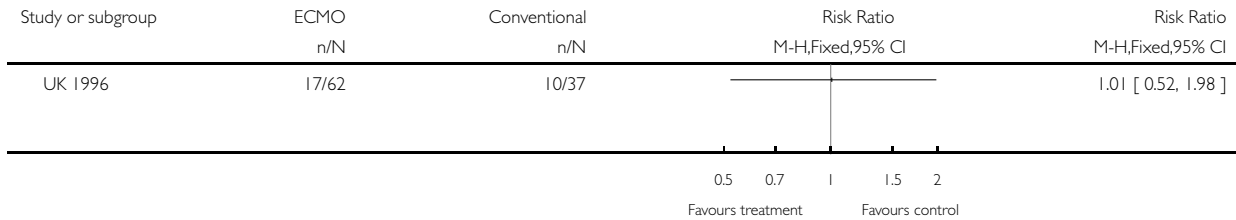


Analysis 1.6. Comparison 1 All eligible infants, Outcome 6 Impairment (with or without disability) in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 6 Impairment (with or without disability) in survivors at one year of age

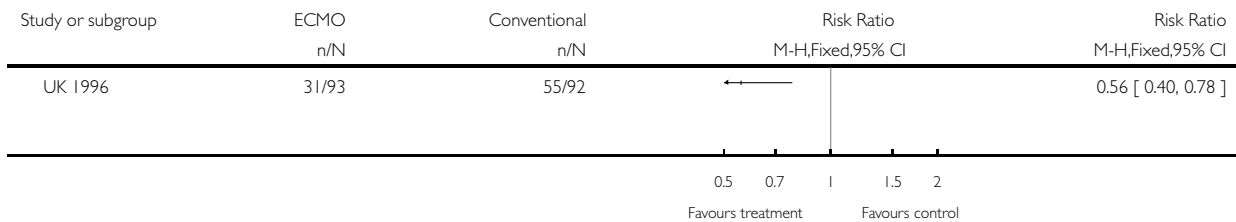


Analysis 1.7. Comparison 1 All eligible infants, Outcome 7 Death or severe disability at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 7 Death or severe disability at one year of age

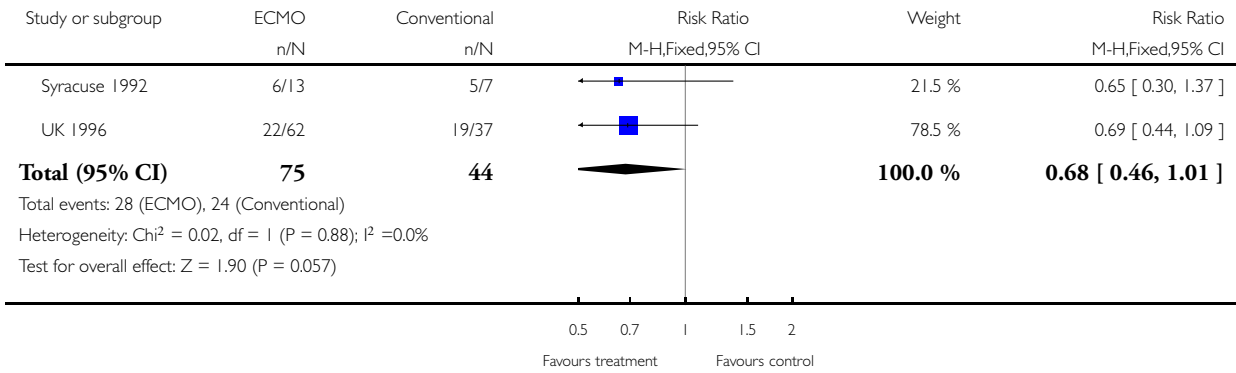


Analysis 1.8. Comparison 1 All eligible infants, Outcome 8 Readmission to hospital in survivors in first year.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 8 Readmission to hospital in survivors in first year

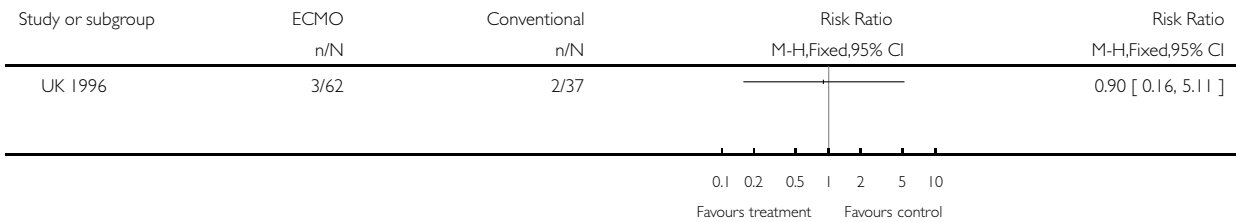


Analysis 1.9. Comparison 1 All eligible infants, Outcome 9 On supplemental oxygen in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 9 On supplemental oxygen in survivors at one year of age

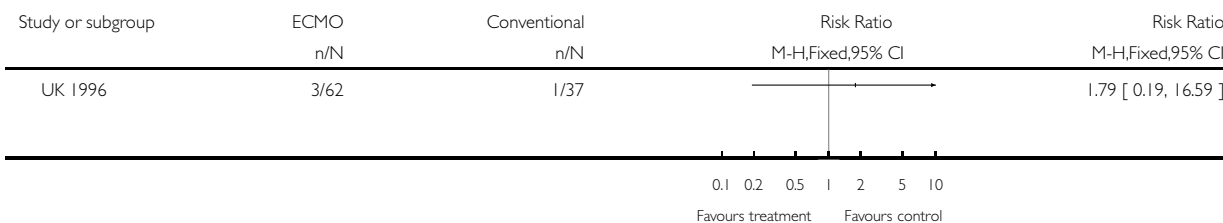


Analysis 1.10. Comparison 1 All eligible infants, Outcome 10 Tube feeding in survivors at one year.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 10 Tube feeding in survivors at one year

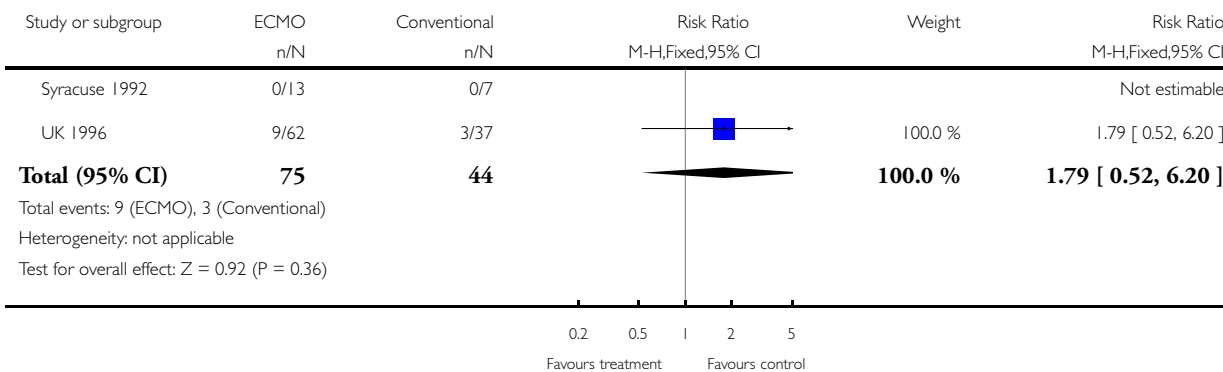


Analysis 1.11. Comparison 1 All eligible infants, Outcome 11 Weight < 3rd centile in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 11 Weight < 3rd centile in survivors at one year of age

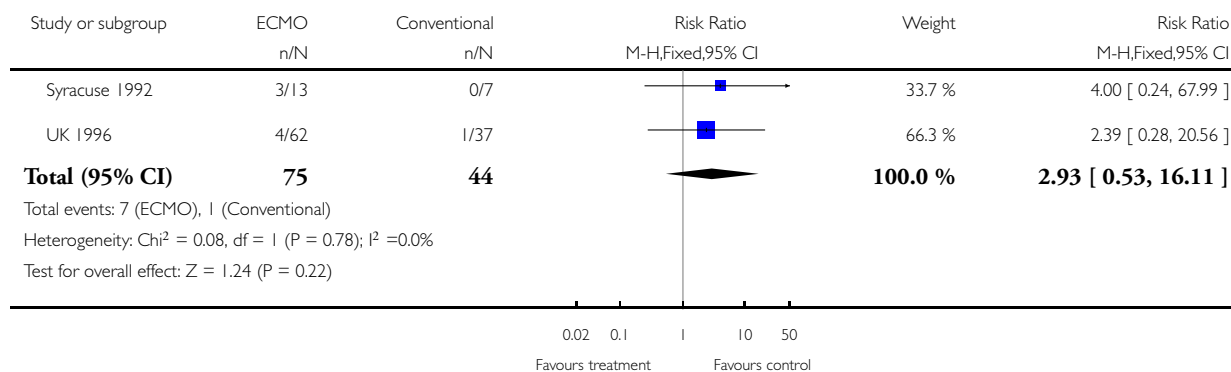


Analysis 1.12. Comparison 1 All eligible infants, Outcome 12 Head circumference < 3rd centile in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 12 Head circumference < 3rd centile in survivors at one year of age

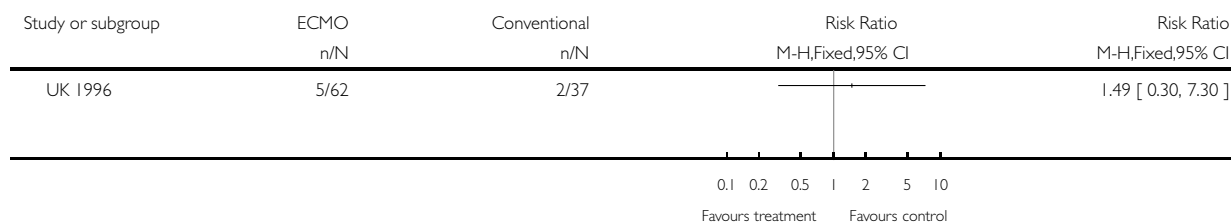


Analysis 1.13. Comparison 1 All eligible infants, Outcome 13 Head circumference > 97th in survivors centile at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 13 Head circumference > 97th in survivors centile at one year of age

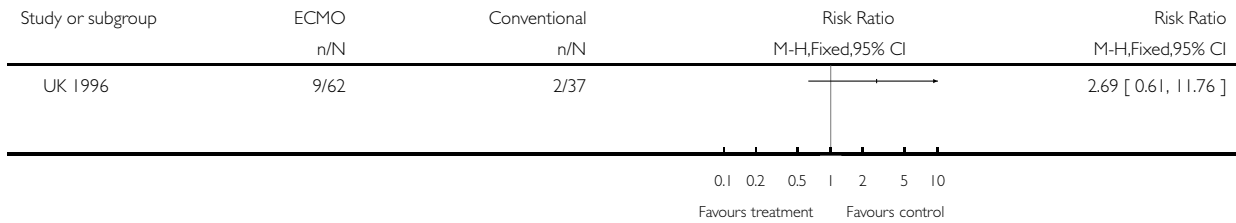


Analysis 1.14. Comparison 1 All eligible infants, Outcome 14 Vision problems in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 14 Vision problems in survivors at one year of age

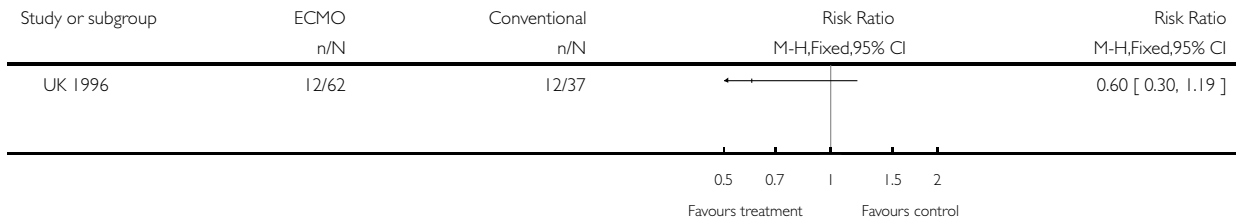


Analysis 1.15. Comparison 1 All eligible infants, Outcome 15 Hearing problems in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 15 Hearing problems in survivors at one year of age

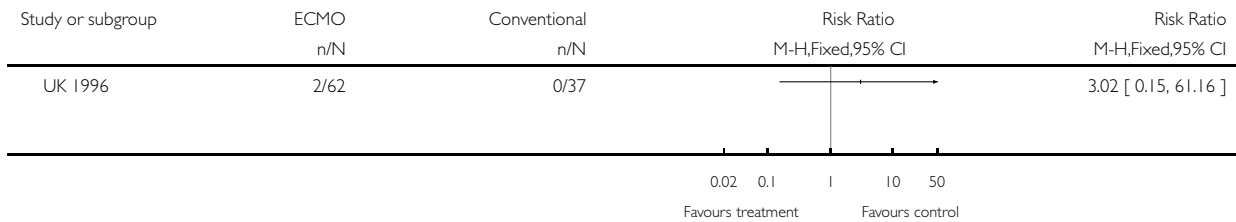


Analysis 1.16. Comparison 1 All eligible infants, Outcome 16 On anticonvulsants in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 16 On anticonvulsants in survivors at one year of age

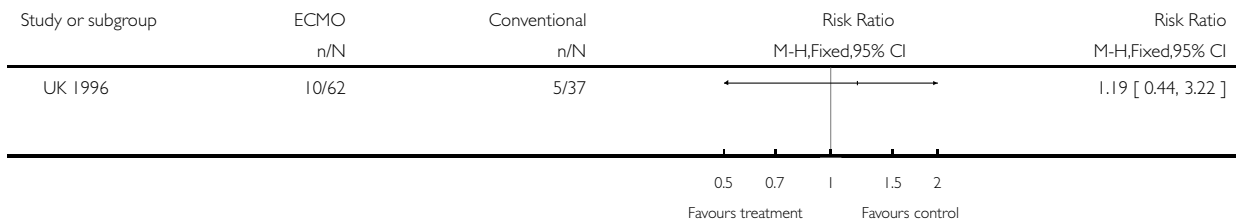


Analysis 1.17. Comparison 1 All eligible infants, Outcome 17 Neuromotor tone changes in survivors at one year.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 17 Neuromotor tone changes in survivors at one year

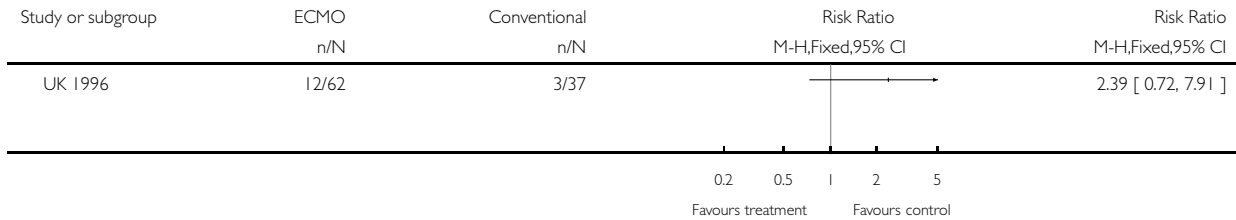


Analysis 1.18. Comparison 1 All eligible infants, Outcome 18 Asymmetrical neuromotor signs in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 18 Asymmetrical neuromotor signs in survivors at one year of age

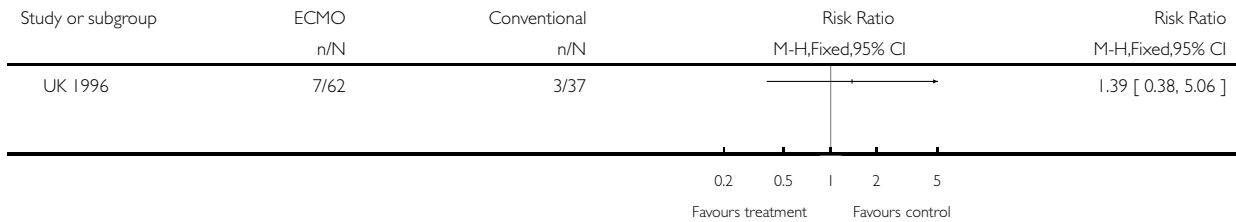


Analysis 1.19. Comparison 1 All eligible infants, Outcome 19 Abnormal axial tone in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 19 Abnormal axial tone in survivors at one year of age

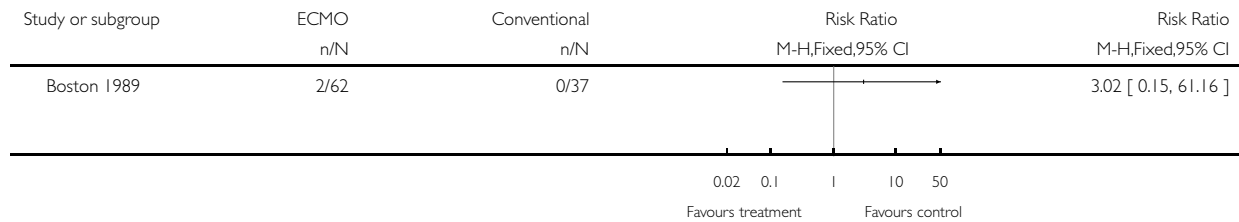


Analysis 1.20. Comparison 1 All eligible infants, Outcome 20 Abnormal movements in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 20 Abnormal movements in survivors at one year of age

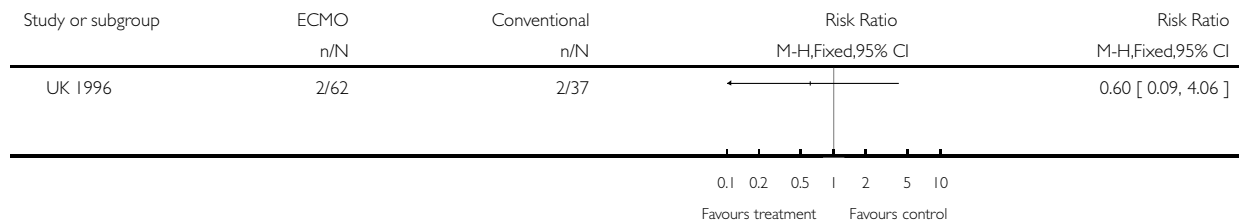


Analysis 1.21. Comparison 1 All eligible infants, Outcome 21 Motor Developmental Quotient less than 50 in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 21 Motor Developmental Quotient less than 50 in survivors at one year of age

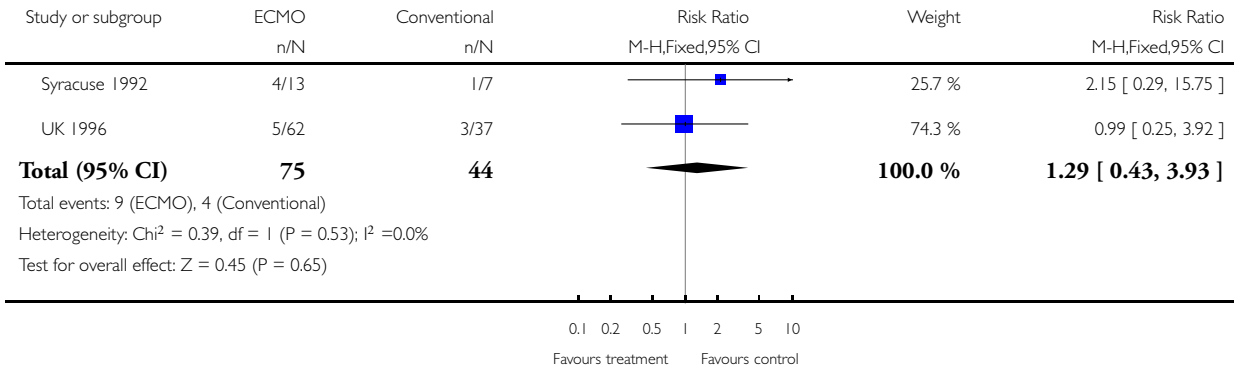


Analysis 1.22. Comparison 1 All eligible infants, Outcome 22 Motor Developmental Quotient less than 70 in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 22 Motor Developmental Quotient less than 70 in survivors at one year of age

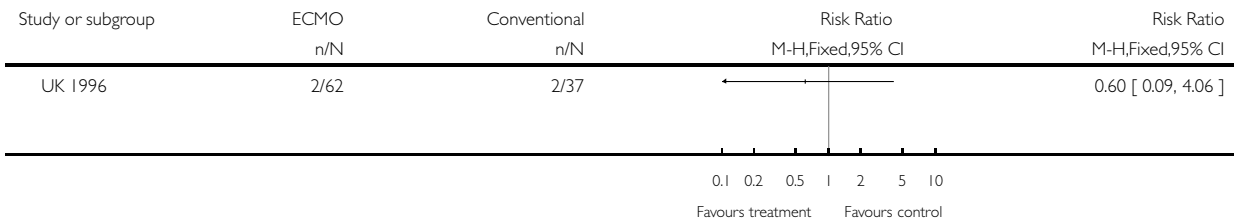


Analysis 1.23. Comparison 1 All eligible infants, Outcome 23 Overall Developmental Quotient less than 70 in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 23 Overall Developmental Quotient less than 70 in survivors at one year of age

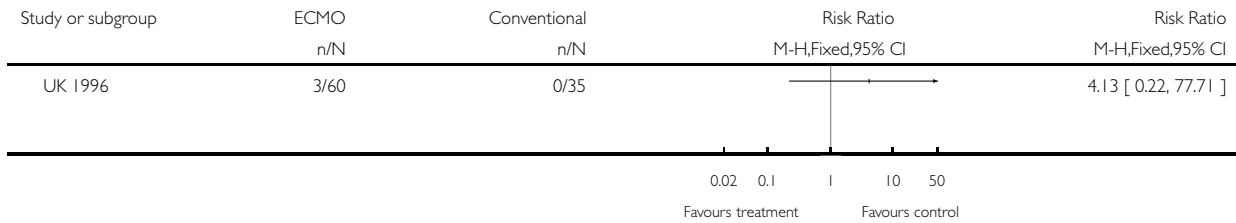


Analysis 1.24. Comparison 1 All eligible infants, Outcome 24 Severe disability in survivors at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 24 Severe disability in survivors at 4 years of age

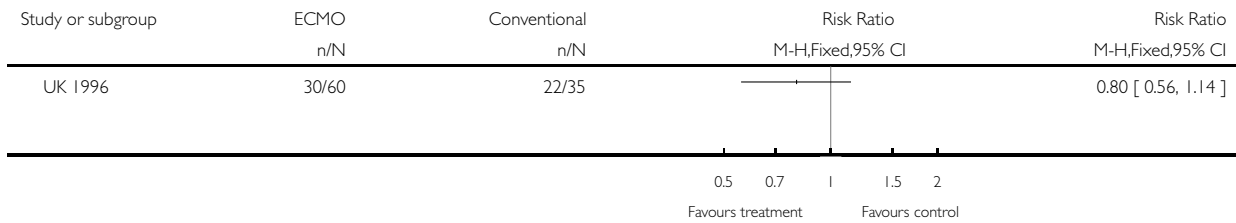


Analysis 1.25. Comparison 1 All eligible infants, Outcome 25 Any disability in survivors at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 25 Any disability in survivors at 4 years of age

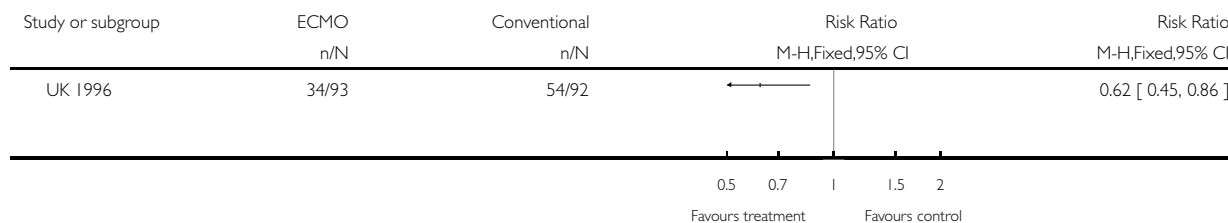


Analysis 1.26. Comparison 1 All eligible infants, Outcome 26 Death or severe disability at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 26 Death or severe disability at 4 years of age

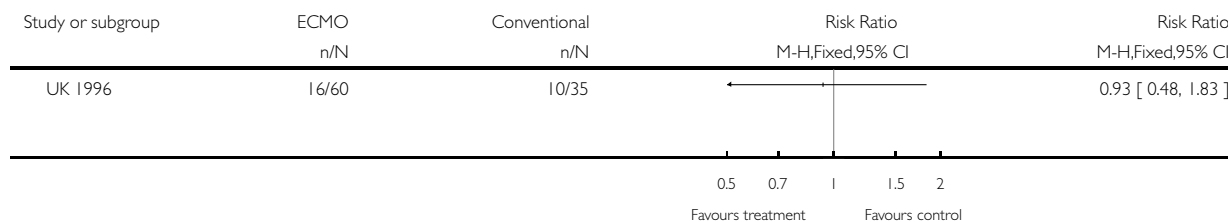


Analysis 1.27. Comparison 1 All eligible infants, Outcome 27 Professional support for special needs in survivors at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 27 Professional support for special needs in survivors at 4 years of age

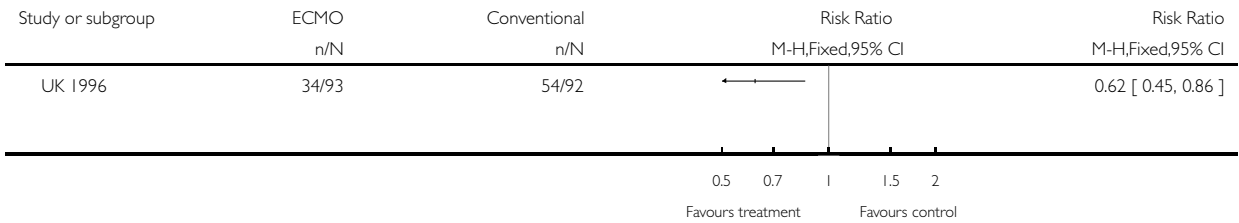


Analysis 1.28. Comparison 1 All eligible infants, Outcome 28 Death or severe disability at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 28 Death or severe disability at 7 years

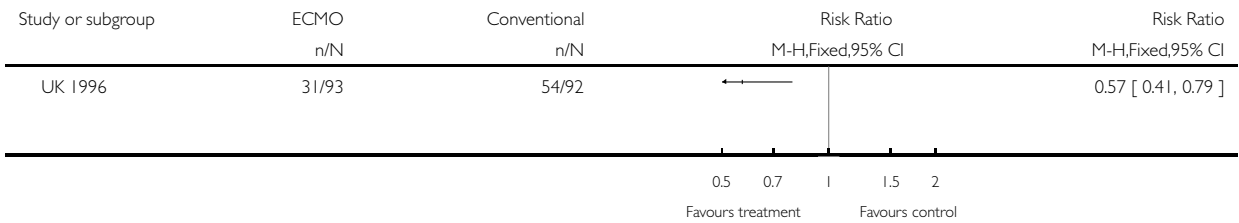


Analysis 1.29. Comparison 1 All eligible infants, Outcome 29 Death by 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 29 Death by 7 years

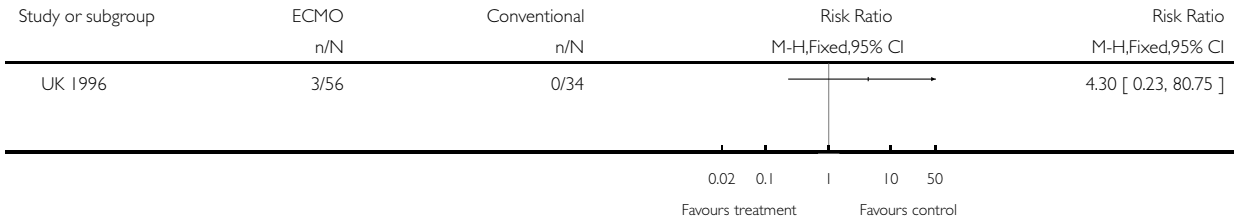


Analysis 1.30. Comparison 1 All eligible infants, Outcome 30 Severe disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 30 Severe disability in survivors at 7 years

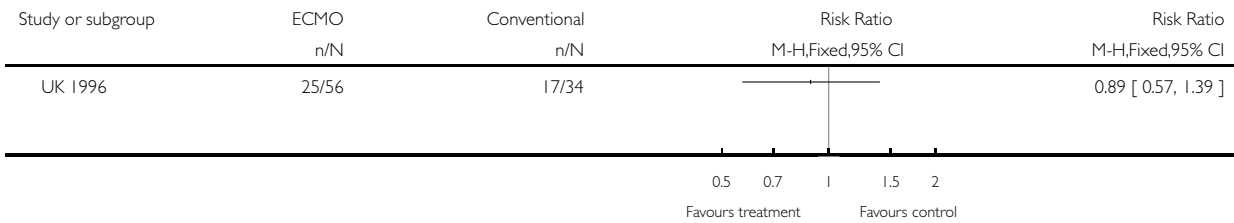


Analysis 1.31. Comparison 1 All eligible infants, Outcome 31 Any disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 31 Any disability in survivors at 7 years

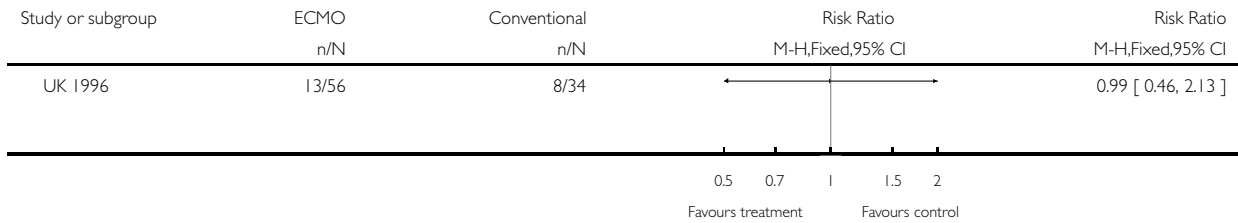


Analysis 1.32. Comparison 1 All eligible infants, Outcome 32 Any cognitive disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 32 Any cognitive disability in survivors at 7 years

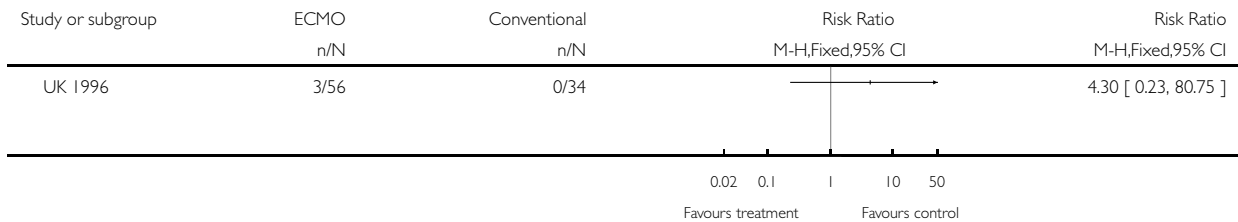


Analysis 1.33. Comparison 1 All eligible infants, Outcome 33 Severe cognitive disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 33 Severe cognitive disability in survivors at 7 years

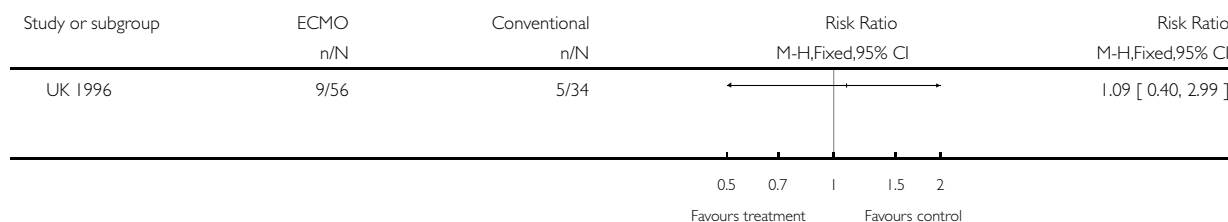


Analysis 1.34. Comparison 1 All eligible infants, Outcome 34 Any neuromotor disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 34 Any neuromotor disability in survivors at 7 years

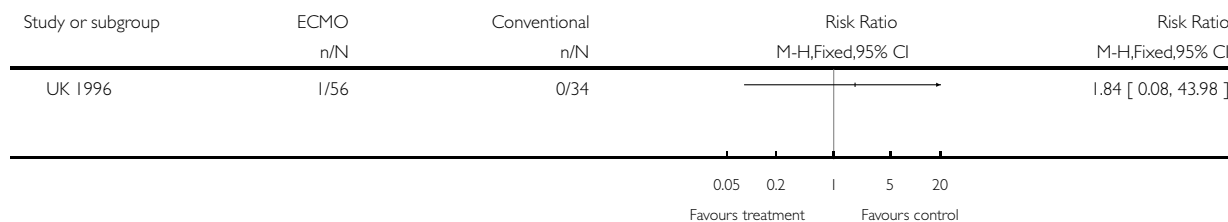


Analysis 1.35. Comparison 1 All eligible infants, Outcome 35 Severe neuromotor disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 35 Severe neuromotor disability in survivors at 7 years

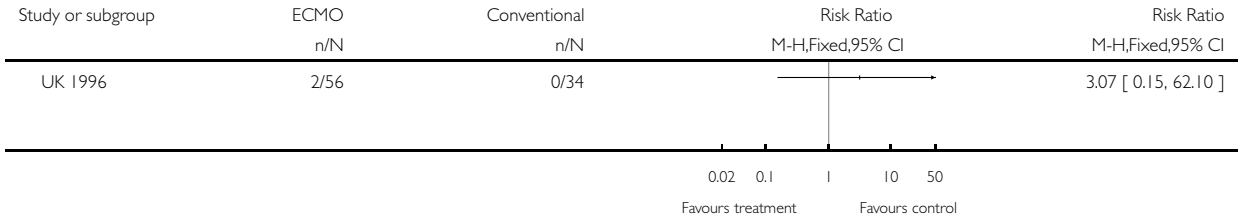


Analysis 1.36. Comparison 1 All eligible infants, Outcome 36 Any general health disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 36 Any general health disability in survivors at 7 years

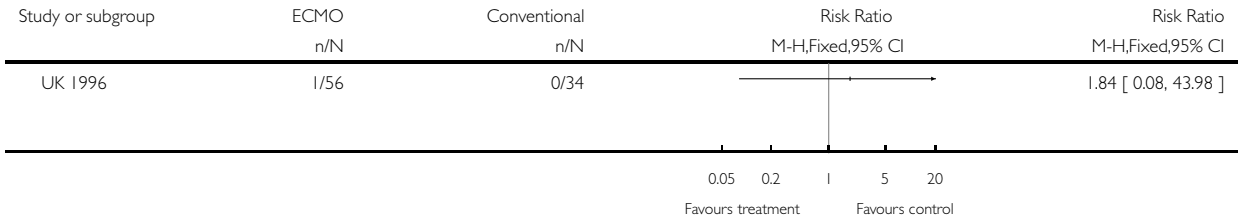


Analysis 1.37. Comparison 1 All eligible infants, Outcome 37 Severe general health disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 37 Severe general health disability in survivors at 7 years

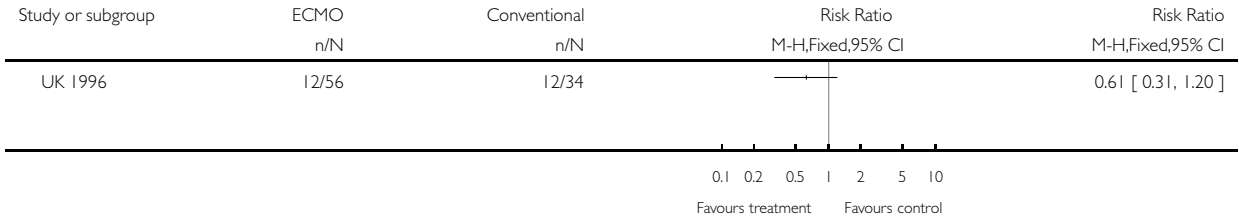


Analysis 1.38. Comparison 1 All eligible infants, Outcome 38 Any behavioural disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 38 Any behavioural disability in survivors at 7 years

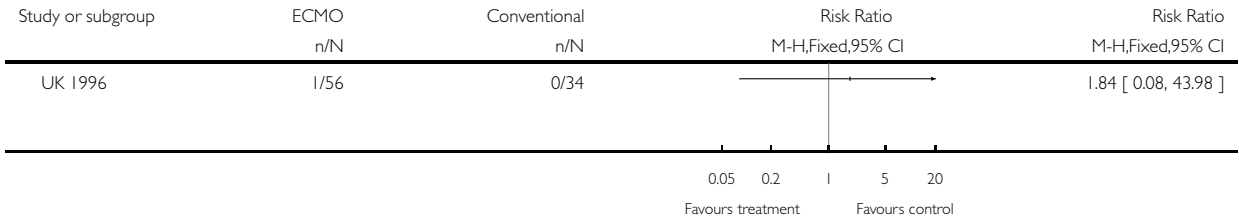


Analysis 1.39. Comparison 1 All eligible infants, Outcome 39 Severe behavioural disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 39 Severe behavioural disability in survivors at 7 years

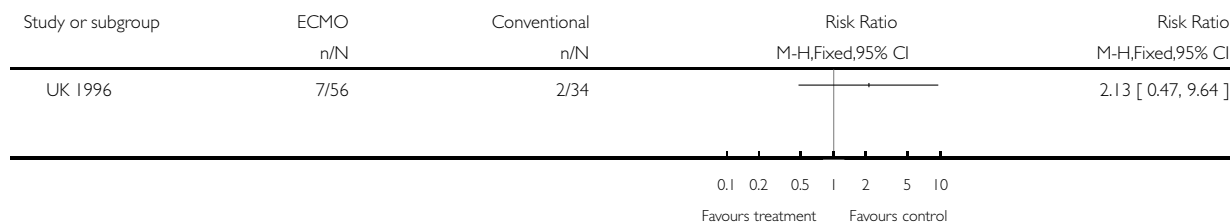


Analysis 1.40. Comparison 1 All eligible infants, Outcome 40 Any visual disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 40 Any visual disability in survivors at 7 years

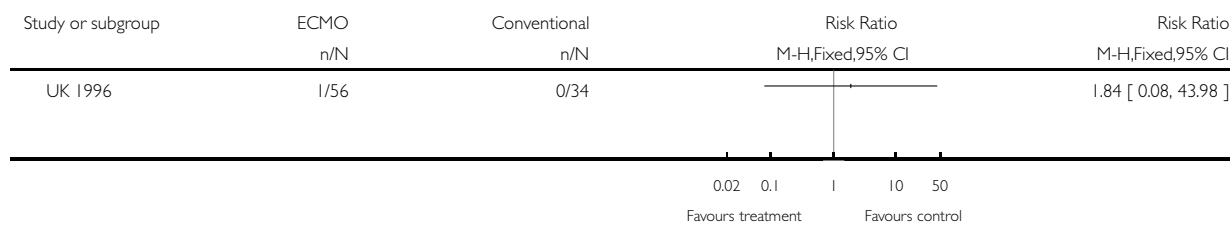


Analysis 1.41. Comparison 1 All eligible infants, Outcome 41 Severe visual disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 41 Severe visual disability in survivors at 7 years

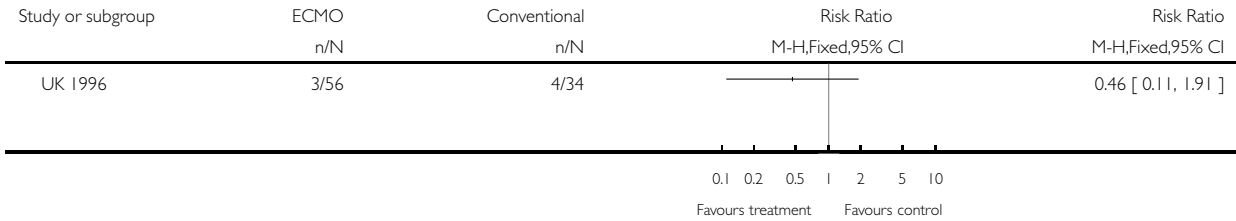


Analysis 1.42. Comparison 1 All eligible infants, Outcome 42 Any hearing disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 42 Any hearing disability in survivors at 7 years

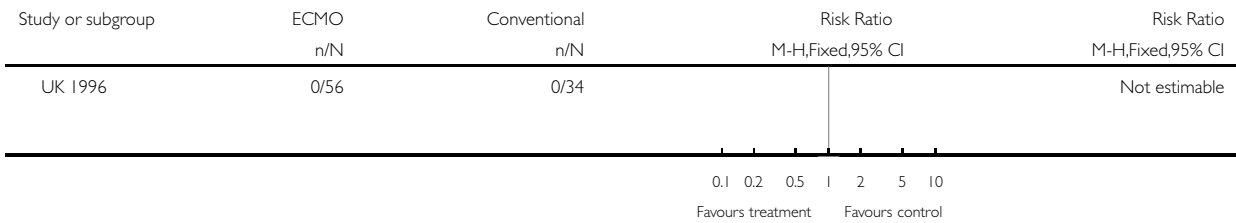


Analysis 1.43. Comparison 1 All eligible infants, Outcome 43 Severe hearing disability in survivors at 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 43 Severe hearing disability in survivors at 7 years

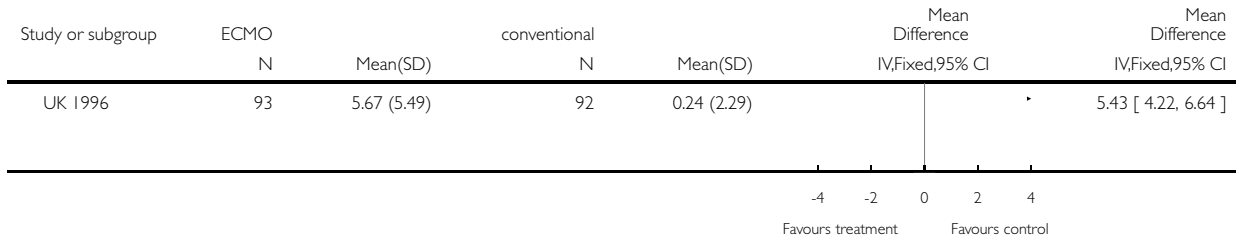


Analysis 1.44. Comparison 1 All eligible infants, Outcome 44 Days on ECMO.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 44 Days on ECMO

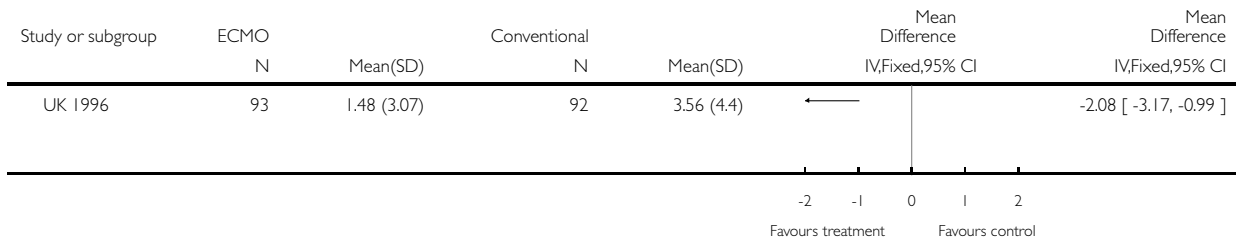


Analysis 1.45. Comparison 1 All eligible infants, Outcome 45 Days on > 90% oxygen.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 45 Days on > 90% oxygen

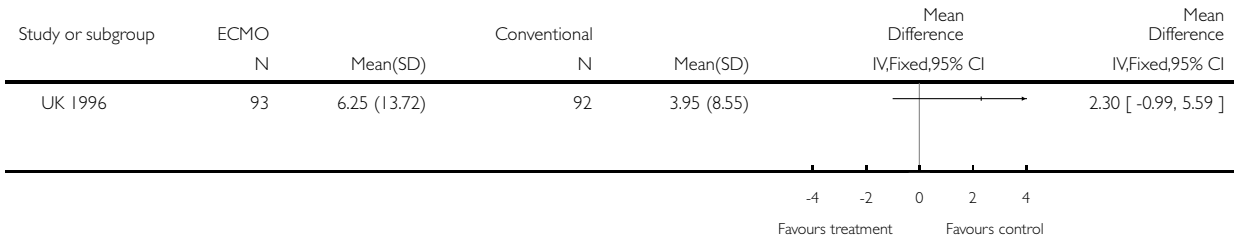


Analysis I.46. Comparison I All eligible infants, Outcome 46 Days on ventilator.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: I All eligible infants

Outcome: 46 Days on ventilator

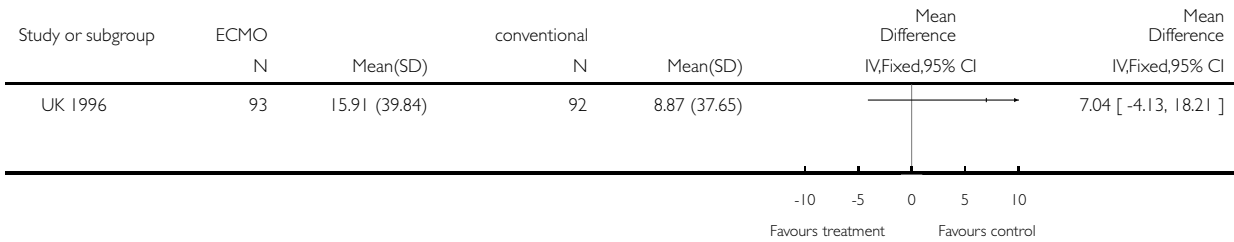


Analysis I.47. Comparison I All eligible infants, Outcome 47 Days on supplementary oxygen at any concentration.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: I All eligible infants

Outcome: 47 Days on supplementary oxygen at any concentration

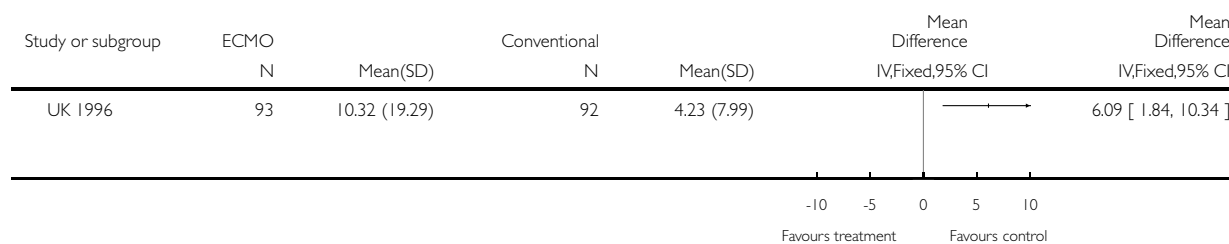


Analysis 1.48. Comparison 1 All eligible infants, Outcome 48 Days on standard neonatal care.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 48 Days on standard neonatal care

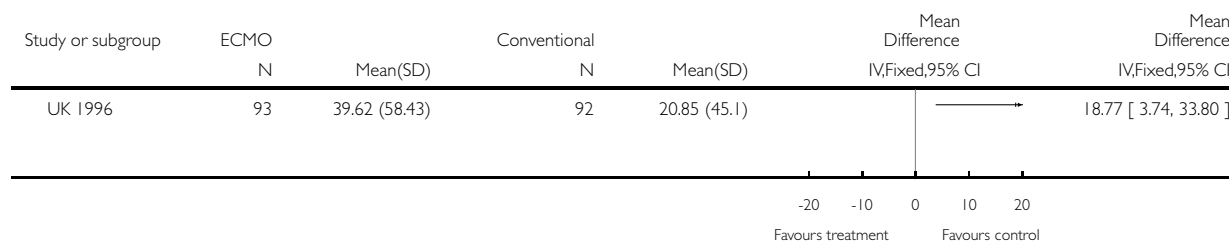


Analysis 1.49. Comparison 1 All eligible infants, Outcome 49 Days in hospital (initial admission).

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 49 Days in hospital (initial admission)

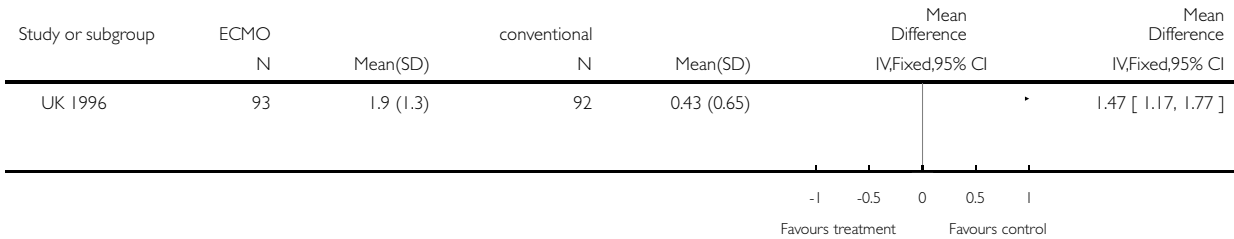


Analysis 1.50. Comparison 1 All eligible infants, Outcome 50 Number of ambulance journeys.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 50 Number of ambulance journeys

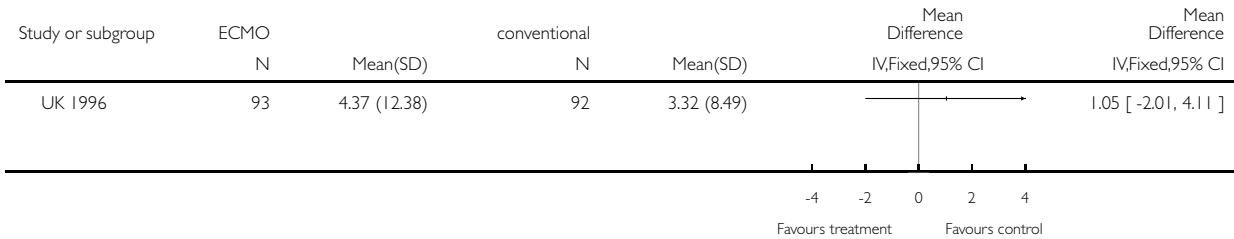


Analysis 1.51. Comparison 1 All eligible infants, Outcome 51 Days in hospital (all re-admissions up to 7 years).

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 51 Days in hospital (all re-admissions up to 7 years)

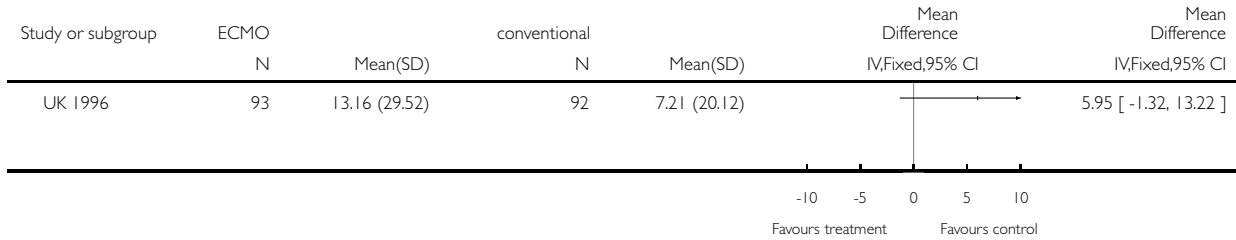


Analysis 1.52. Comparison 1 All eligible infants, Outcome 52 Number of hospital outpatient visits up to 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 52 Number of hospital outpatient visits up to 7 years

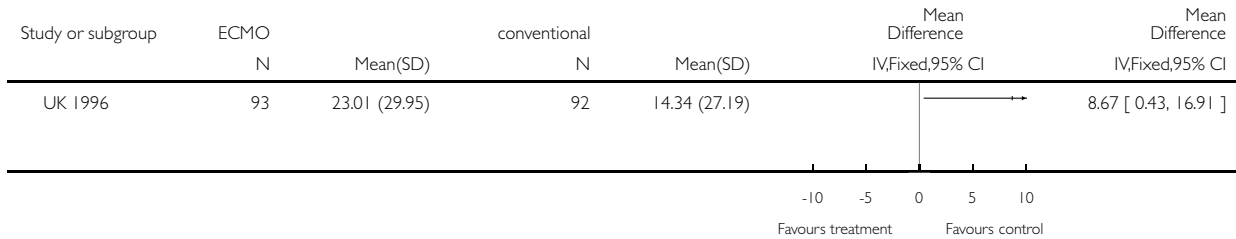


Analysis 1.53. Comparison 1 All eligible infants, Outcome 53 Number of family doctor visits up to 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 53 Number of family doctor visits up to 7 years

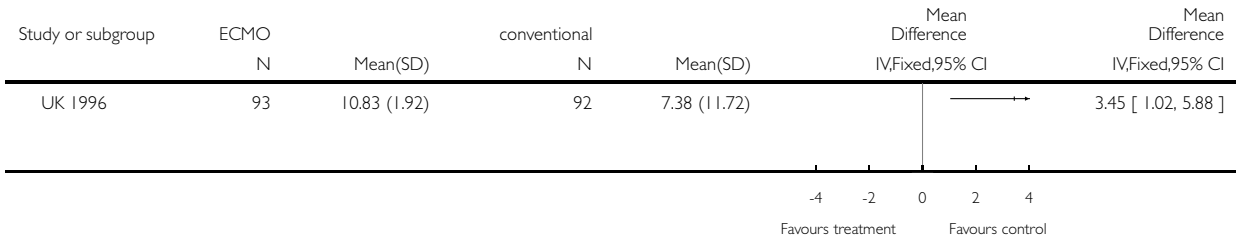


Analysis I.54. Comparison I All eligible infants, Outcome 54 Number of health visitor visits up to 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: I All eligible infants

Outcome: 54 Number of health visitor visits up to 7 years

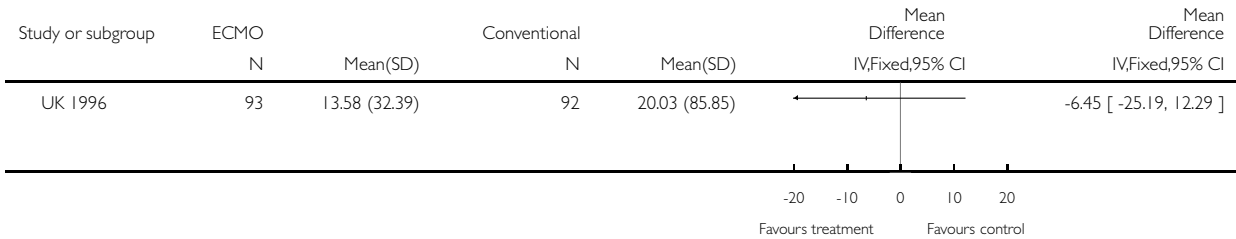


Analysis I.55. Comparison I All eligible infants, Outcome 55 Number of visits by other professionals up to 7 years.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: I All eligible infants

Outcome: 55 Number of visits by other professionals up to 7 years

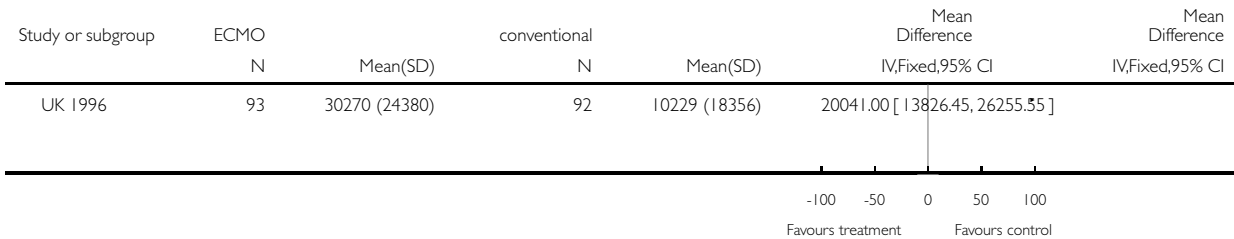


Analysis 1.56. Comparison 1 All eligible infants, Outcome 56 Total health service costs (£GB 2003 prices).

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 56 Total health service costs (£ GB 2003 prices)

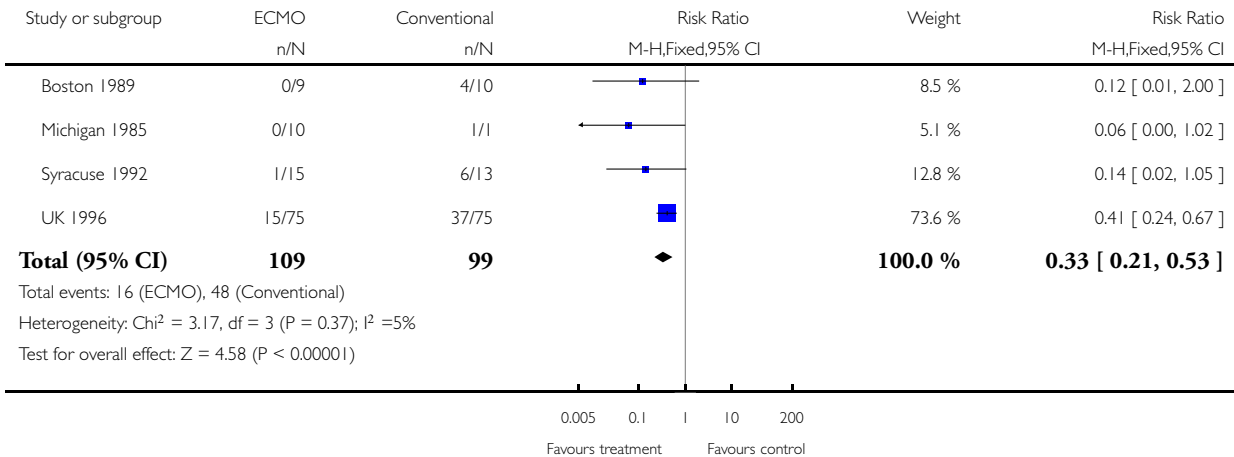


Analysis 2.1. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 1 Death before discharge home.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 1 Death before discharge home

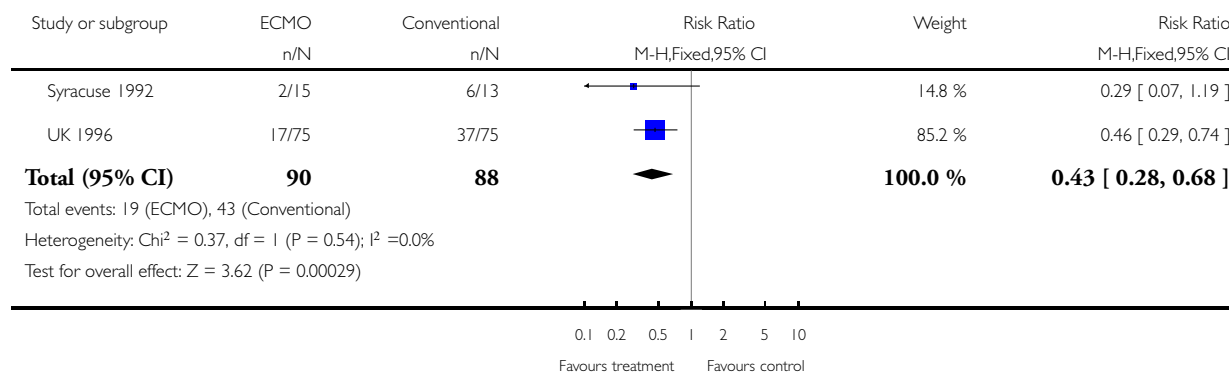


Analysis 2.2. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 2 Death in the first year of life.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 2 Death in the first year of life

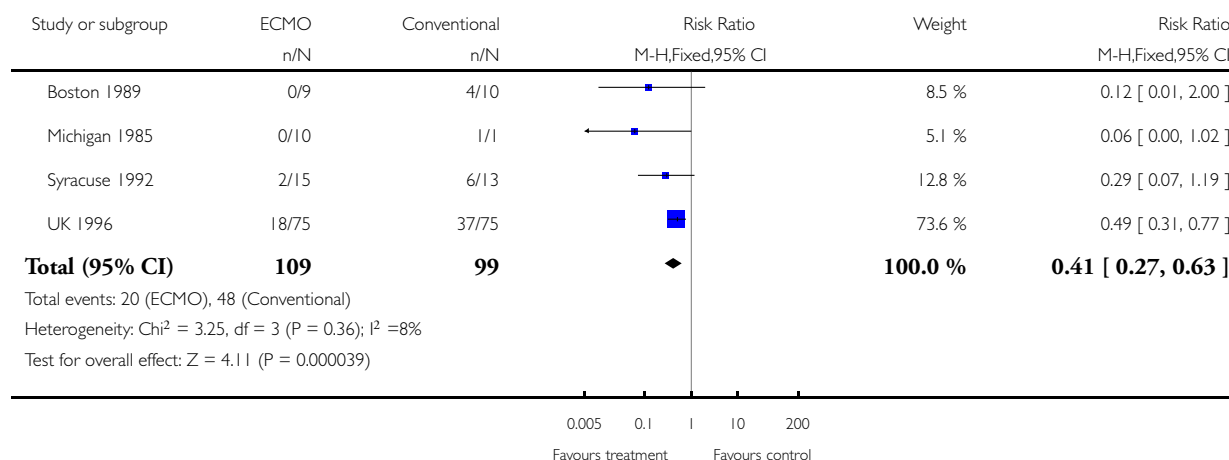


Analysis 2.3. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 3 Death at any time to the end of data collection.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 3 Death at any time to the end of data collection

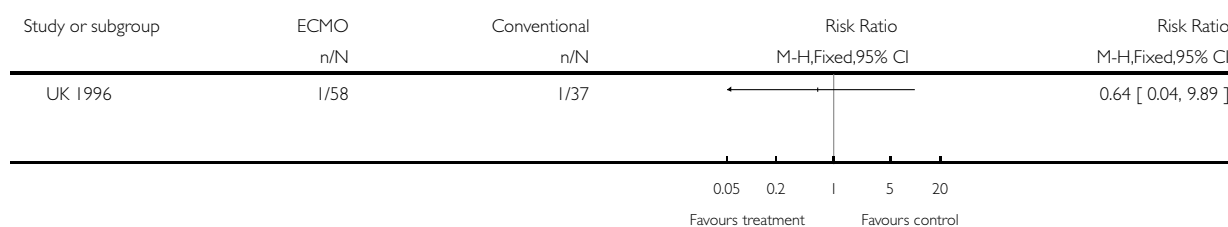


Analysis 2.4. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 4 Severe disability in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 4 Severe disability in survivors at one year of age

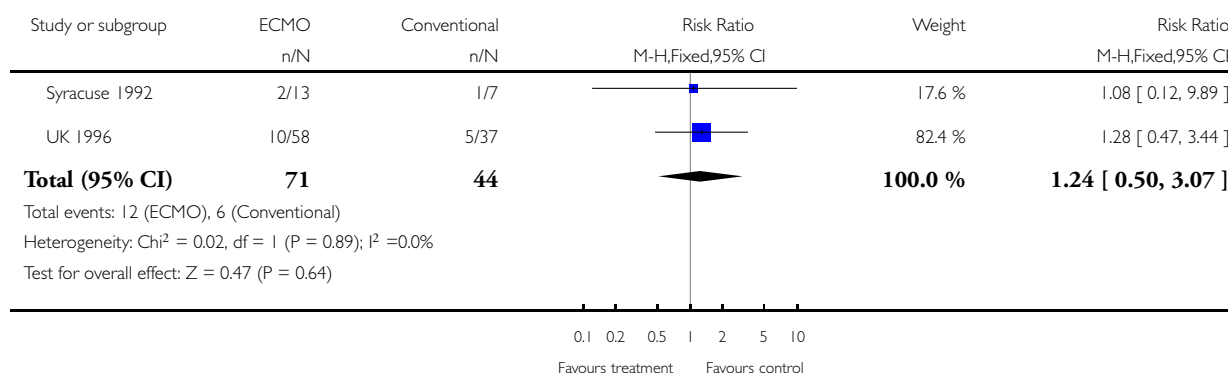


Analysis 2.5. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 5 Disability (severe and not severe) in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 5 Disability (severe and not severe) in survivors at one year of age

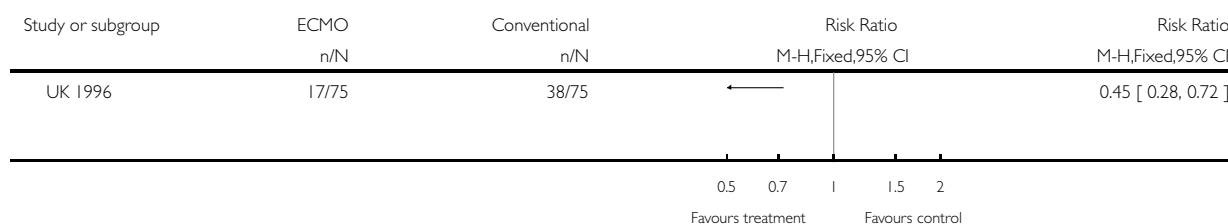


Analysis 2.6. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 6 Death or severe disability at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 6 Death or severe disability at one year of age

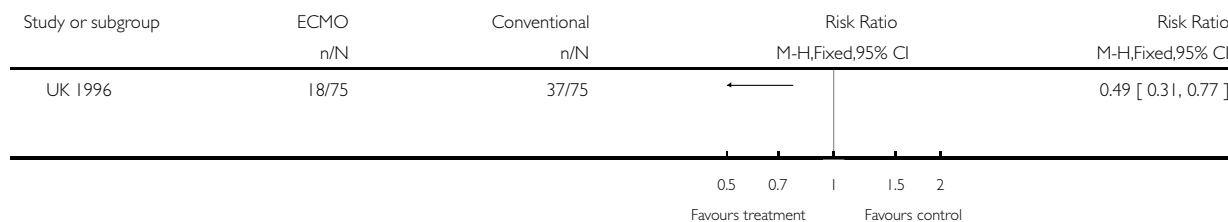


Analysis 2.7. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 7 Death or severe disability at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 7 Death or severe disability at 4 years of age

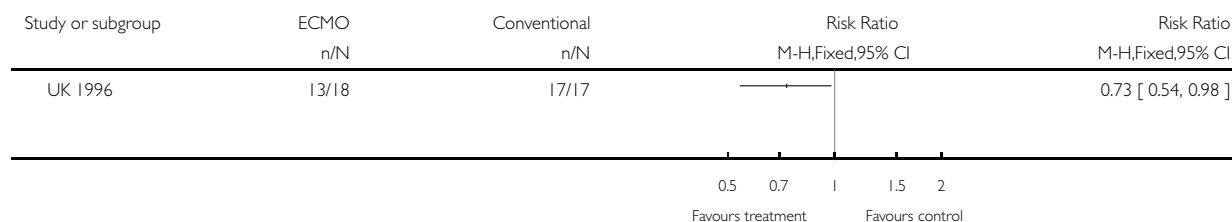


Analysis 3.1. Comparison 3 Infants with congenital diaphragmatic hernia as principal diagnosis, Outcome 1 Death before discharge home.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 3 Infants with congenital diaphragmatic hernia as principal diagnosis

Outcome: 1 Death before discharge home

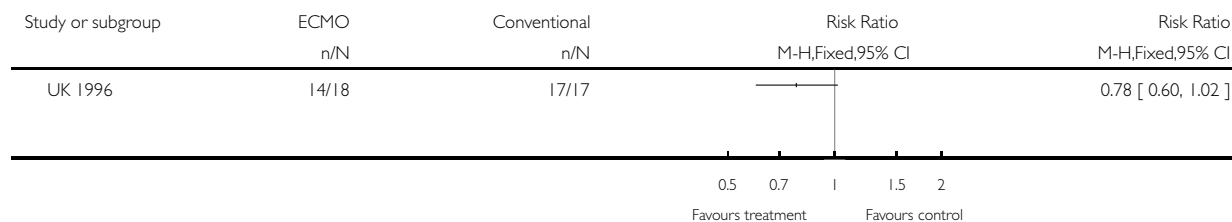


Analysis 3.2. Comparison 3 Infants with congenital diaphragmatic hernia as principal diagnosis, Outcome 2 Death in the first year of life.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 3 Infants with congenital diaphragmatic hernia as principal diagnosis

Outcome: 2 Death in the first year of life

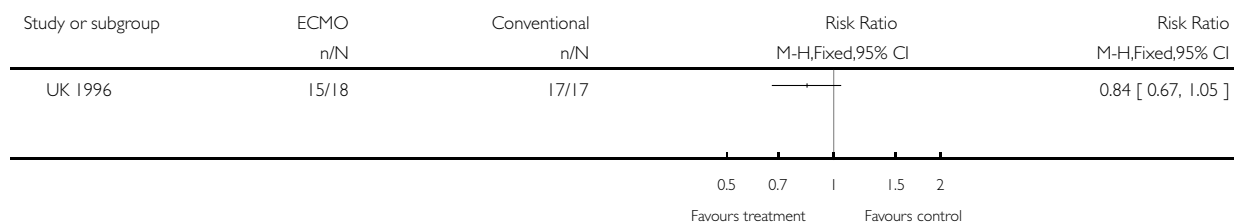


Analysis 3.3. Comparison 3 Infants with congenital diaphragmatic hernia as principal diagnosis, Outcome 3 Death at any time to the end of data collection.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 3 Infants with congenital diaphragmatic hernia as principal diagnosis

Outcome: 3 Death at any time to the end of data collection

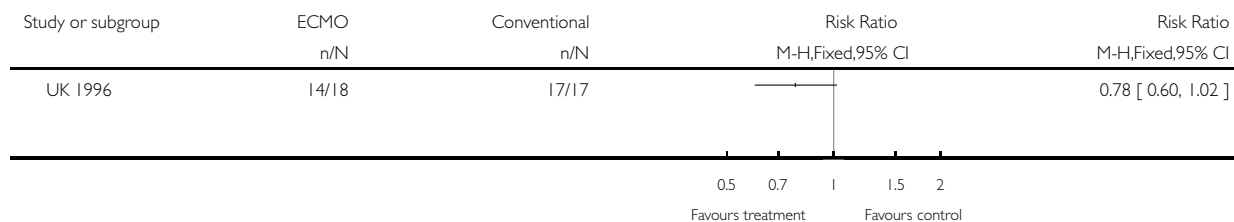


Analysis 3.4. Comparison 3 Infants with congenital diaphragmatic hernia as principal diagnosis, Outcome 4 Death or severe disability at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 3 Infants with congenital diaphragmatic hernia as principal diagnosis

Outcome: 4 Death or severe disability at one year of age

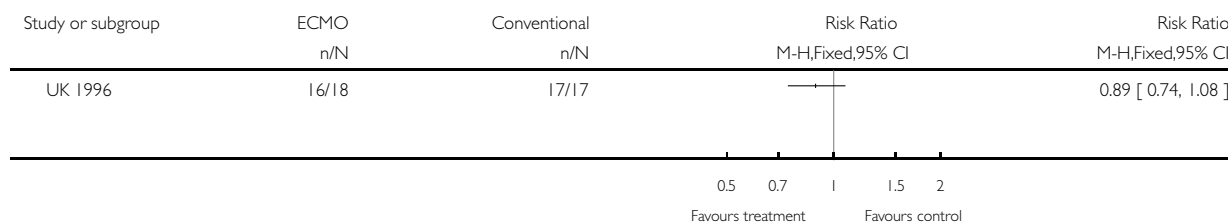


Analysis 3.5. Comparison 3 Infants with congenital diaphragmatic hernia as principal diagnosis, Outcome 5 Death or severe disability at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 3 Infants with congenital diaphragmatic hernia as principal diagnosis

Outcome: 5 Death or severe disability at 4 years of age

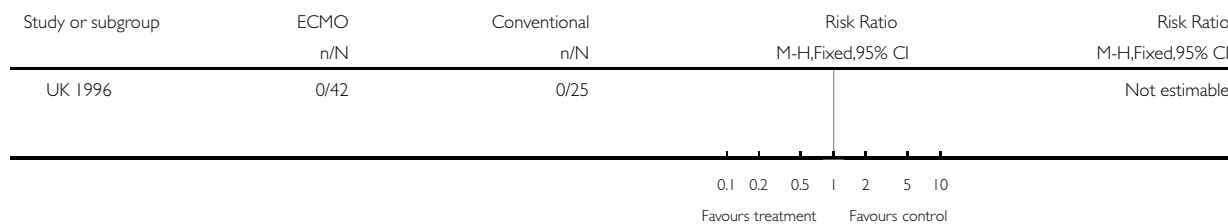


Analysis 4.1. Comparison 4 Infants with oxygenation index 40-60 at trial entry, Outcome 1 Severe disability in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 4 Infants with oxygenation index 40-60 at trial entry

Outcome: 1 Severe disability in survivors at one year of age

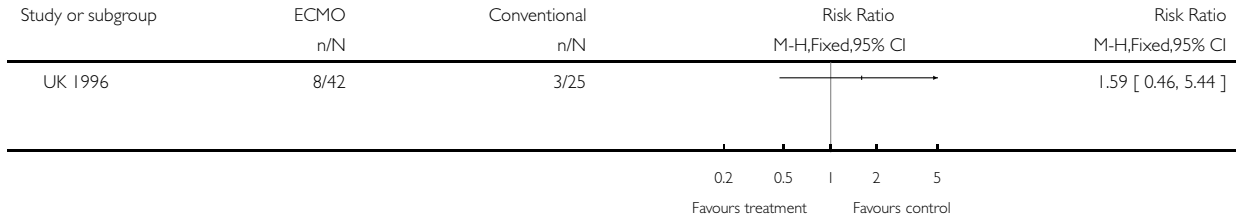


Analysis 4.2. Comparison 4 Infants with oxygenation index 40-60 at trial entry, Outcome 2 Disability (severe and not severe) in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 4 Infants with oxygenation index 40-60 at trial entry

Outcome: 2 Disability (severe and not severe) in survivors at one year of age

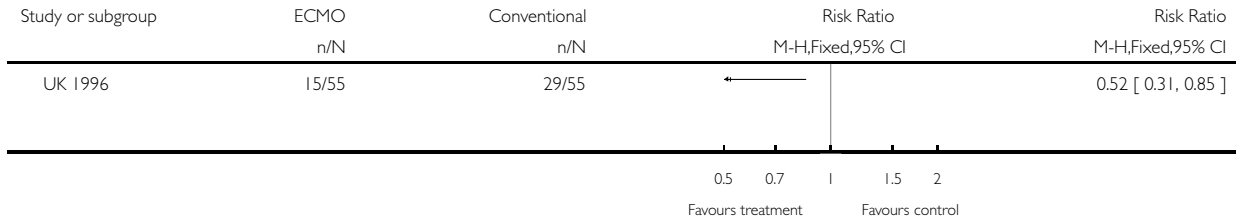


Analysis 4.3. Comparison 4 Infants with oxygenation index 40-60 at trial entry, Outcome 3 Death or severe disability at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 4 Infants with oxygenation index 40-60 at trial entry

Outcome: 3 Death or severe disability at 4 years of age

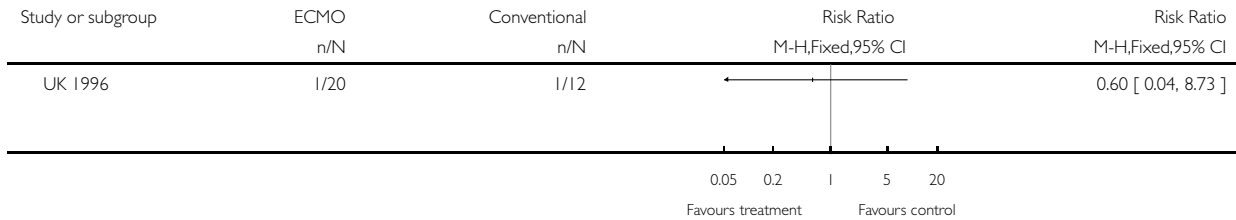


Analysis 5.1. Comparison 5 Infants with oxygenation index > 60 at trial entry, Outcome 1 Severe disability in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 5 Infants with oxygenation index > 60 at trial entry

Outcome: 1 Severe disability in survivors at one year of age

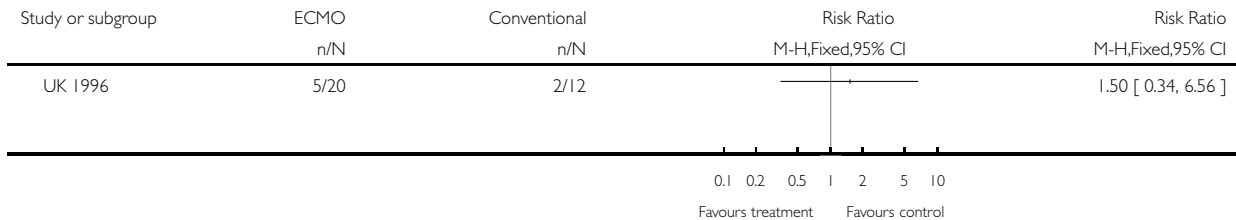


Analysis 5.2. Comparison 5 Infants with oxygenation index > 60 at trial entry, Outcome 2 Disability (severe and not severe) in survivors at one year of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 5 Infants with oxygenation index > 60 at trial entry

Outcome: 2 Disability (severe and not severe) in survivors at one year of age

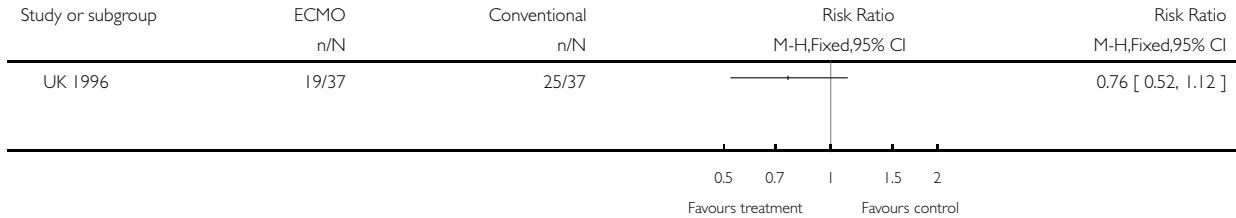


Analysis 5.3. Comparison 5 Infants with oxygenation index > 60 at trial entry, Outcome 3 Death or severe disability at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 5 Infants with oxygenation index > 60 at trial entry

Outcome: 3 Death or severe disability at 4 years of age



WHAT'S NEW

Last assessed as up-to-date: 1 November 2007.

Date	Event	Description
10 March 2008	Amended	Converted to new review format.
2 November 2007	New search has been performed	This updates the review "Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants" published in The Cochrane Database of Systematic Reviews, Issue 1, 2002 (Elbourne 2002). Based on an updated search in November 2007, no new trials have been reported, but there is new data on clinical follow up data at seven years (including resource use) from the largest trial
2 November 2007	New citation required but conclusions have not changed	The conclusion that ECMO is an effective intervention for eligible babies is not changed by the new data: ECMO increases survival without severe disability. Although overall resource use is also increased, cost effectiveness, estimated for the UK context, is within the accepted range for neonatal technologies

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 1, 2002

CONTRIBUTIONS OF AUTHORS

All: Reading and extracting data from papers retrieved

All: Writing and editing text

DE: statistics expertise

MM: economics expertise

DF: clinical expertise

DECLARATIONS OF INTEREST

The authors of this Review are authors of one of the trials which will be included in the Review

SOURCES OF SUPPORT

Internal sources

- University of East Anglia (HEFCE), UK.
- University of Leicester (HEFCE), UK.
- London School of Hygiene and Tropical Medicine (HEFCE), UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Extracorporeal Membrane Oxygenation; Infant, Newborn; Randomized Controlled Trials as Topic; Respiratory Insufficiency [mortality; *therapy]

MeSH check words

Humans