Scottish Government Health Directorates

The provision of non-H1N1 adult respiratory Extra Corporeal Membrane Oxygenation (ECMO) in the medium and longer term for Scotland

ECMO Expert Group

Report and recommendations December 2009
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EXECUTIVE SUMMARY

The role of ECMO in critical care

1. Extra-Corporeal Membrane Oxygenation (ECMO) provides temporary life support to patients with severe but potentially reversible cardiac or respiratory failure. It may also be used to assist the transition from cardiopulmonary bypass to ventilation after heart surgery.

2. ECMO is an approved and commissioned treatment for neonatal and paediatric cardiac and respiratory failure and is currently provided in 4 centres in the UK, including Yorkhill Hospital in Glasgow. There remain risks associated with the treatment but improved management plans and equipment have greatly reduced these.


4. The place of ECMO in adult treatment has been less well established. It is used for cardiac support in association with cardiac surgery, particularly transplantation, but its role as an intervention for patients with severe respiratory failure and the corresponding evidence base for this has been less clear. This was the area on which the Expert Group was established to report.

5. The CESAR trial evaluated the clinical and cost effectiveness of ECMO for adults with severe respiratory failure. The Group acknowledges the limitations of both the study and the associated Health Technology Assessment (HTA), which are detailed in Chapter 2. However, it represents the most comprehensive randomised controlled trial undertaken on adult respiratory ECMO and it reported a survival benefit for patients referred to an ECMO centre compared to those who received conventional management. The Group has therefore concluded that there is sufficient clinical and economic evidence to recommend that Scottish patients should continue to have access to ECMO.

6. With regard to safety, although this treatment carries overt risks, extracorporeal circuits are now relatively widely used in critical care and whilst there is likely to be a learning curve for a new centre, the technical requirements and clinical skills to provide ECMO are now well understood. Existing designated ECMO centres have been supportive of the development of any new centres, and so there is no reason in principle why a service for adults could not be established in Scotland.

7. The Expert Group received consistent advice that an ECMO centre should aim to treat at least 10 adult patients per year to ensure patient safety and to maintain clinical expertise. An assessment of the potential future demand for this treatment in Scotland is therefore key to deciding whether a Scottish centre would be viable. This has been a challenge for the Group, because of the paucity of epidemiological data and stable population-based comparators, as well as the unknown long term influence of the H1N1 pandemic, the results of the CESAR trial and the potential future improvements in conventional ventilation techniques.
8. However, the Group estimated that about 10 to 12 adult patients in Scotland each year would require treatment with respiratory ECMO, which would make it feasible to establish a service in Scotland or to continue to take part in UK arrangements. The cost of establishing a new service in Scotland for between 10 and 12 adult patients would be approximately £1.5m to £1.8m per year, with additional one-off set up costs of approximately £445K. This is compared with a cost of continuing access to the UK’s service as it stands at present of between £0.9m and £1.1m per year.

9. Patients who require ECMO for respiratory failure will be those who have failed to respond to conventional ventilatory management but who are deemed to have potential for survival. Expert evidence has strongly suggested that a service should be based in a general critical care unit which can provide whole-system care for these patients. It was considered that intensivists were best placed to manage the patients but that on-site access to cardiothoracic surgical skills and perfusionists should also be considered key.

10. A full spectrum of supporting facilities is required, including imaging, laboratory and blood transfusion, as well as compliance with Extracorporeal Life Support Organisation (ELSO) guidelines for the management of patients and staff training. Outcomes should be discussed and shared with other centres, and submitted to the ELSO Registry to ensure that the highest quality of care is provided to patients. Any new centre should also collaborate with other centres in order to share experience, support and advice, and to alleviate pressures on capacity in times of high demand.

11. There were differing views on the transportation of patients requiring ECMO. Some experts believe that patients should be stabilised and transported on ECMO, whilst others feel that transportation to the service on conventional ventilation is sufficient. However it was agreed that any ECMO service should provide a safe and appropriate form of assessment and retrieval service and the Group shares this view.

Recommendations

12. The Group therefore makes the following recommendations to the Cabinet Secretary as the basis for making a decision on the future provision of adult respiratory ECMO for the population of Scotland:

1. The Expert Group believes that there is sufficient evidence to support the efficacy, safety and clinical effectiveness of ECMO for adult patients with potentially reversible advanced respiratory failure.

2. Patients from Scotland therefore should have continued access to this treatment.

3. The Group recommends that in order to be clinically effective and safe, any adult respiratory ECMO service requires to treat a minimum of 10 patients a year. It is likely that the potential demand for adult respiratory ECMO in
Scotland will be between 10 and 12 patients a year. However there is uncertainty about this figure and future trends.

4. It is therefore feasible to establish an adult respiratory ECMO service in Scotland, which would cost approximately £1.5m to £1.8m per year, with additional one-off set up costs of approximately £445K. However, the alternative is to continue to access facilities provided at a UK level through the nationally commissioned service at Leicester, the cost of which would be between £0.9m and £1.1m per year.

5. An adult respiratory ECMO service requires to be led by a committed intensivist and located within a general intensive care environment capable of providing a range of respiratory interventions and with access to the range of specialties required by critically ill patients.

6. An adult respiratory ECMO service also requires to provide a safe form of assessment and retrieval service which ensures patients can be transported safely. The Group recognises the challenges for a new unit of transporting patients on ECMO but recommends that a service aspires to do this.

7. The Group recommends that a small volume service such as adult respiratory ECMO should be provided to international standards and should participate in a collaborative network with other adult respiratory ECMO centres in order to manage fluctuations in demand and to ensure clinical excellence.

13. Members stand ready to provide any further advice to the Cabinet Secretary for Health and Wellbeing on aspects of implementation of these recommendations if required and as appropriate.
CHAPTER 1: INTRODUCTION

Background: Expert Group

1. At the request of the Cabinet Secretary for Health & Wellbeing, the Expert Group was established in October 2009 to consider the medium and longer term provision of adult respiratory Extra Corporeal Membrane Oxygenation (ECMO) in Scotland beyond the current H1N1 pandemic.

2. The Group’s remit was:

- To consider the findings of the recent CESAR trial and other published evidence for the use of ECMO in adults;
- To take evidence from leading experts regarding the efficacy and safety of ECMO treatment in adults and its relationship to other established treatments for advanced respiratory failure, recognising the current and likely future requirements of the Scottish population for such treatment; and
- Having considered this evidence, to provide recommendations to the Cabinet Secretary for Health & Wellbeing regarding current and future ECMO provision in Scotland.

3. Membership of the Group is contained in Appendix 1.

Working methods

4. The Group fulfilled its remit by:

- Commissioning NHS Quality Improvement Scotland to produce a report reviewing published evidence on adult respiratory ECMO;
- Developing a standardised questionnaire for experts to complete (included in Appendix 3) and interviewing colleagues with an interest in and/or experience of adult respiratory ECMO within Scotland and in the UK, Australia, Sweden and Ireland;
- Visiting adult respiratory ECMO centres in Glenfield Hospital, Leicester and the Karolinska Institute, Stockholm;
- Undertaking a needs assessment using Scottish data and based on comparative analysis; and
- Reviewing and discussing key issues at Group meetings and/or teleconferences as required.

5. In addition, the Group has maintained links with the Department of Health and the UK National Commissioning Group which are similarly working on the issue of medium and long term provision of ECMO in England and Wales.

ECMO – definition and development

6. ECMO is a technique in which a patient’s blood is removed from the body and circulated, by means of a pump, across an artificial membrane before being returned to the patient. In this process, the blood is oxygenated and carbon dioxide removed.
The technique performs an artificial heart/lung function, and as such can provide heart and/or lung support.

7. For the purpose of this report, the ECMO technique considered is that which provides lung (respiratory) support rather than cardiac support. The process may be required for days or weeks and is highly intensive in terms of staffing and technical support.

8. ‘Respiratory' ECMO was developed in the 1970s from techniques originally used in the context of cardiac surgery as part of heart-bypass processes. The technique has been shown in clinical trials to be of value for neonatal and paediatric patients with certain conditions. It is also employed for patients as a ‘bridge’ before and after heart/lung transplantation.

9. There are theoretical attractions to the use of ECMO to treat respiratory failure in adults, but the evidence of benefit has been much less clear-cut. This is covered in chapter 2. Nevertheless, ECMO has been used for a myriad of acute lung injury processes including Adult Respiratory Distress Syndrome (ARDS), massive pulmonary embolus, pneumonia and traumatic lung injury. All of these conditions are characterized by the severity of hypoxaemia (failure of oxygenation), impaired ventilation (failure to adequately remove carbon dioxide) or both.

10. Conventional intensive care management is appropriate for most patients suffering from even the most serious manifestations of the conditions set out above. Intensive care has developed rapidly and the key role of the properly trained intensivist is now established. Improvements in understanding and ventilator equipment mean that a number of options are now available for treatment of such patients and the specific technique(s) used will depend upon the nature of the underlying condition and the patient’s response to the treatments chosen. These interventions and the general management of the patient require to be performed in an adequately staffed and resourced Intensive Care environment by a multi-disciplinary team led by senior and experienced practitioners.

11. Irrespective of the underlying cause, all ECMO practitioners agree that its use is only valid in the context of a disease process which is potentially recoverable and which is unresponsive to conventional intensive care procedures.

Referral and treatment

12. Experts who provide ECMO emphasised the importance of viewing respiratory ECMO as one of a range of interventions to provide respiratory support for patients with potentially reversible conditions, when conventional ventilation has not proved either possible or effective.

13. Experts were however keen to emphasise that ECMO should be considered as a positive intervention at an appropriate time during the patient care pathway, rather than as a ‘last resort’ intervention in an attempt to rescue a patient who is dying as outcomes are likely to be poor.
14. The optimal time for instituting ECMO treatment in an individual patient is therefore unclear. Most specialists argue that early referral is preferred, to minimise lung damage, and previous evidence suggested outcomes were poor in patients who had been ventilated for more than a week. Some units now consider this too restrictive. The approach taken clearly has the potential to influence the number of patients treated.

Criteria for referral

15. A variety of scoring-type systems (e.g. the Murray Score) which attempt to quantify the severity of respiratory failure have been used to assist the decision to refer for, or commence, ECMO. It is clear that in practice decisions are based on clinical experience and an assessment of each patient. Experts emphasised the importance of making such assessments following close observation and a judgement of the potential risks of treatment against potential benefits.

16. Central to the decision to use ECMO in a patient is the presence of potentially reversible lung pathology. Some centres have specific inclusion and exclusion criteria for referrals, a sample of which can be found in Appendix 5.

Type of treatment and run time

17. The average ‘run time’ for a patient on ECMO is around 10 days (although the period of time for which ICU care will be required will be considerably longer). The primary determinant of ECMO duration is the nature of the underlying lung condition and its response to therapy. Longer ECMO treatments for up to 50-60 days can be associated with good outcomes.

18. The method by which blood is removed from and returned to the body varies from centre to centre. The specific technique is determined by individual patient characteristics and the experience/background of the staff involved.

Stepping down/withdrawal of treatment

19. Clinicians confirmed to the Group that situations occur when ECMO is no longer offering a realistic chance of recovery and that treatment should be withdrawn. However, for patients who improve, the process of weaning from ECMO treatment may be complex and requires detailed assessments of respiratory adequacy.

20. The importance of step-down post-ECMO Intensive Care Unit (ICU) care, including its multi-disciplinary nature and uncertain duration, was emphasised by all parties. Specialists feel that patients need to stay in the ECMO centre for several days following discontinuation of ECMO. This is one of several key reasons that ECMO is carried out in the context of ongoing specialist Intensive Care expertise.

Current UK provision of Respiratory ECMO for Children

21. Respiratory ECMO in neonates and children is provided as an integral part of the Paediatric Intensive Care Service commissioned on behalf of NHSScotland by
the National Services Division (NSD) of NHS National Services Scotland. The Royal Hospital for Sick Children at Yorkhill in Glasgow is one of 4 units in the UK which offer Paediatric ECMO, alongside Leicester, Newcastle and Great Ormond Street, London. These units work as a network to provide care when it is clinically required across the UK.

**Current UK provision of Respiratory ECMO for Adults**

22. There is currently 1 adult respiratory ECMO facility in the UK. This unit was commissioned by the UK National Commissioning Group to assess the clinical and cost effectiveness of respiratory ECMO care for adults. The unit is based at Glenfield Hospital in Leicester. Through UK National Specialist Commissioning arrangements, managed in Scotland by NSD, adult patients from across the UK are referred to Leicester for ECMO. Leicester also works in partnership with the European ECMO centre in Stockholm, Sweden.

**H1N1 Influenza**

23. Due to H1N1, the number of patients treated worldwide with respiratory ECMO in 2009 has been significantly greater than any previous year. This illness has been unusual in 2 important ways:

- Severe hypoxemia has been more common than in most other critical illnesses.
- The outcome for H1N1 patients treated with ECMO has been significantly better than is normal for patients treated with respiratory ECMO prior to H1N1. This has been confirmed by statistics from both the Leicester and Stockholm centres.

24. Clinicians in centres in Australia which provided respiratory ECMO to a large number of H1N1 patients during the Australasian winter of 2009 have noted a higher rate of cerebral haemorrhage in this group, which is now being studied.

25. Overall, many patients with H1N1 have been successfully treated with ECMO therapy and the publicity surrounding the role of ECMO in achieving these good outcomes has raised both patient and professional expectations of what the treatment can provide. The CESAR trial was conducted prior to the H1N1 pandemic. This trial, together with other evidence is examined in the following chapter.
CHAPTER 2 : ECMO EVIDENCE BASE

26. There is clear evidence of the efficacy of respiratory ECMO for neonates and children with specific conditions including meconium aspiration, infection, and congenital diaphragmatic hernia.

27. However, the evidence base surrounding the efficacy and safety of respiratory ECMO for adults with ARDS to date has been less clear. It has been the subject of a range of published papers since the 1970s, but NICE considered that there was insufficient evidence to justify a recommendation in 2002. A Health Technology Assessment\(^1\) (HTA) has subsequently been funded by the National Institute for Healthcare Research (NIHR), and has been published in shortened form as the CESAR trial in September 2009.\(^3\)

28. In addition to the Group’s own analysis, the Scottish Health Technologies Group of NHS Quality Improvement Scotland (NHS QIS) was asked to review and analyse available evidence in greater depth. The methodology and full report are available in Appendix 7.

29. During the course of conducting the review, NHS QIS noted that the term ‘ECMO’ is variously and inconsistently used interchangeably with related terms such as Extra Corporeal Life Support (ECLS) and Extra Corporeal Lung Assist (ECLA). This variation in the use of terminology may mean that some relevant evidence not described in the literature as ‘ECMO’ may have been missed. Nonetheless the Expert Group found that similar themes emerged from its own analysis, that of NHS QIS and external expert opinion.

30. In addition, evidence was taken from clinicians practising ECMO with regards to the critical mass required to ensure that ECMO may be provided to the required level of quality and safety. This follows at paragraphs 51 – 52.

Clinical effectiveness

Previous Randomised Controlled Trials (RCTs)

31. Well conducted RCTs are considered to provide the best quality of evidence. Two earlier RCTs (published in 1979 and 1994) showed no significant improvement

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\(^1\) Elbourne, D et al. ‘NIHR Health Technology Assessment Programme: Conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR)’. HTA ref. 99/01/01. Unpublished. Project abstract available from www.hta.ac.uk/1150

\(^2\) This project was funded by the NIHR Health Technology Assessment programme and will be published in full in Health Technology Assessment. See the HTA programme website for further project information. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

in survival with ECMO. Both reported a high incidence of bleeding and both were stopped early.

32. NHS QIS considers that the relevance of data on the incidence of complications in studies undertaken before and during the 1990s (including the early RCTs) is probably limited. Developments in ECMO technology over time have reduced the risk of complications and the Expert Group accepted the consensus that these trials are not relevant to current practice because of advances in both ECMO and other intensive care management.

Non-randomised studies

33. A number of non-randomised prospective studies were published between 1976 and 2007, generally reporting poorer survival outcomes in ECMO patients. Case series published in the same period reported survival to discharge rates of between 10% to 100% (median 53%). Most recently, investigators in Australia and New Zealand have reported an inception cohort study of all admissions to their ICUs due to infection with influenza A(H1N1) during June to August 2009 and a case series describing 68 patients treated with ECMO for influenza-associated severe ARDS. The Expert group note that non-randomised studies are highly susceptible to unintentional bias and should not be used as primary evidence to support or dismiss a treatment.

34. There are few data on long-term outcomes following ECMO for respiratory failure in adults, and those which do exist do not provide information about long term outcomes among patients who receive conventional care.

35. In summary, the Expert Group concluded that it is not possible to consider them as an evidence base in the context of the clinical effectiveness of respiratory ECMO in adults compared with conventional treatment.

CESAR trial

36. The clinical and cost effectiveness of ECMO in adults with severe respiratory failure as compared with conventional management has been most effectively evaluated in the CESAR RCT, conducted by the UK national ECMO centre at Glenfield Hospital in Leicester for the purposes of the HTA funded by the NIHR. This multicentre trial randomised 180 adults to receive either conventional ventilatory support or transfer to the specialist centre for consideration for ECMO. The primary outcome measure was survival without severe disability. This was 16% higher for patients in the ECMO referral group over conventional management, suggesting that one additional patient would benefit for every 6 patients treated.

37. Reaction to the results of the trial has been divided, as predicted in an accompanying editorial published in *The Lancet* on 16 September 2009. Some see the positive result as confirmation of the safety and effectiveness of ECMO.

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compared with conventional management, whilst others suggest that the limitations of the trial prevent any meaningful conclusions being drawn.

38. The Expert Group recognises that the trial has limitations. It was undertaken on an ‘intention to treat’ basis, which is correct in terms of study design but not all of the patients allocated to ECMO actually received ECMO treatment, and the rate of survival among those who were referred for ECMO but who did not receive it was the same as those who received ECMO. There were incomplete follow up data for three patients in the control group and that could be sufficient to change the findings. There were other differences in treatment between the ECMO and control groups which might have affected outcome including the use of steroids and Molecular Albumin Recycling System (MARS).

39. In terms of applicability, the Expert Group shares the view of NHS QIS, the HTA and of *The Lancet* editorial that a major limitation of the CESAR study is the lack of standardisation in conventional management techniques provided to patients in the control group, due to a lack of agreement amongst participating hospitals on what constituted ‘optimal’ care. NHS QIS cautioned that without knowing whether management in the control group reflected treatment in Scottish ICUs the applicability of the results to Scotland was uncertain, although the Expert Group considers that treatment in Scotland is similar to that in the rest of the UK. In addition, patients were referred to a single ECMO-capable hospital, and therefore the outcomes achieved here may not be generalisable to other hospitals with ECMO capability.

40. The Group however agrees with comments made by NHS QIS and the authors of the HTA that the trial was well conducted in terms of internal validity and recognises that design flaws with regards to standardising conventional management were a pragmatic response to the lack of agreement amongst participating units. The techniques reflect those used every day throughout ICUs in the UK for patients with ARDS and the Group agrees with the analysis of the HTA that without this pragmatism, the study could not have proceeded.

41. In addition, the trial included and reflected the risks posed by transport, which are undoubtedly high for such critically ill patients.

42. The Expert Group concludes that, on balance, the CESAR trial provides sufficient evidence to indicate that in selected patients ECMO could be a clinically effective treatment.

**Safety**

43. ECMO complications are mainly those associated with cannulation, anticoagulation and circuit disruptions. Risks to the patient include perforation of blood vessels during cannulation, bleeding, heparin-induced thrombocytopenia, infection and haemolysis.

44. In the CESAR trial one participant suffered fatal vessel perforation during percutaneous cannulation and two died in transit to the specialist centre, one from catastrophic pulmonary haemorrhage and the other due to the failure of the oxygen
supply in the ambulance. There is some evidence from retrospective observational studies that inter-hospital transfer on mobile ECMO systems may improve survival, and this view was supported by a number of clinicians involved in the provision of ECMO.

**Economics**

45. The CESAR trial investigators evaluated whether ECMO for severe adult respiratory failure was cost-effective and used decision modelling to estimate the utility gain over a predicted lifetime.

46. The additional average health care cost per patient referred for ECMO was such that the overall cost was more than double the average cost of conventional management. Patients allocated to consideration for ECMO incurred average total costs of £73,979 compared to £33,435 for conventional management, a difference of £40,544. However, the authors considered that referral for ECMO resulted in a lifetime predicted incremental cost per QALY of £19,000 (95% Confidence Interval £7,622 to £59,200).

47. The Group notes the recommendations of the HTA that local economic models need to be developed to assess cost-effectiveness in different contexts and that further research is needed to develop robust models that take account of geographical location (including costs of transport), economies of scale and long-term quality of life.

48. However, no other economic evaluations of adult respiratory ECMO were identified and so the Group agrees with the assessment made by NHS QIS and the HTA that whilst the cost of providing ECMO is double that of providing conventional ventilatory treatment, the lifetime prediction of cost-utility of £19,000 per QALY is within acceptable levels and therefore that respiratory ECMO for adults may be taken to be cost-effective.

**Conclusion**

49. Apart from the CESAR trial and 2 earlier RCTs, and excluding individual care reports, the evidence for adult respiratory ECMO support comprises mainly observational data from cohorts and case series.

50. The Group recognises the limitations and criticisms of the CESAR trial, but accepts it as the best available and primary evidence base. It recognises that trials of newer ventilatory techniques are awaited and that these have not been compared directly with ECMO. It recognises that better trials would be very difficult to conduct and are unlikely to be undertaken for several years, if at all. The Expert Group was convened precisely because the evidence is equivocal and a judgement is required. On balance therefore the Group considers that the CESAR trial demonstrates that referral of patients with respiratory failure to a specialist ECMO capable centre could be clinically effective and may be taken to be cost effective.
Additional evidence: critical mass

51. ELSO standards require that ECMO centres should be located in geographic areas that can support a minimum of 6 ECMO patients per centre per year and that “the cost effectiveness of providing fewer than 6 cases per year combined with the loss, or lack of clinical expertise associated with treating fewer than this number of patients per year should be taken into account when developing a new program”.

52. This has been confirmed by clinicians working in ECMO centres. The Group recorded a general consensus from clinicians that 10 cases per year represented the minimum number of cases required to ensure patient safety and to maintain clinical skills.
CHAPTER 3: MODELLING DEMAND

53. Any decision on the medium and longer term provision of adult respiratory ECMO in Scotland is dependent upon the potential demand which might exist for such a service.

Difficulties of modelling demand

54. This is extremely difficult to model, given that referrals are made by individual clinicians, based upon judgements of individual clinical need, awareness of the range of treatments available for patients with severe respiratory distress and individual judgements of their efficacy. Specific data for the potential demand for adult respiratory ECMO in Scotland does not therefore currently exist.

55. Prior to the H1N1 pandemic, the provision of ECMO for adult respiratory support had been considered as rare and highly specialised and for many years, clinicians have also lacked a clear evidence base on the efficacy and cost effectiveness of ECMO as an intervention compared with conventional ventilation.

56. The majority of experts contacted by the Group emphasised the prominent role that respiratory ECMO has played during the H1N1 pandemic and the positive outcomes which have been achieved for patients as key factors which will raise awareness of, and, therefore demand for, ECMO as an interventional therapy. In addition, the publication of the CESAR trial has raised the profile of ECMO amongst clinicians.

57. It is likely that clinicians, patients and their relatives are now more aware of the potential benefits of ECMO and whilst demand for this treatment may drop to a level lower than that witnessed during the pandemic, it is likely to be higher than before the pandemic for a range of non-H1N1 patients. This has been confirmed by evidence from some of the clinicians in the Australian units most heavily involved in providing ECMO for H1N1 patients, which suggests that demand has returned to a steady state but that the level is somewhat higher than pre-H1N1 – in some hospitals, it is more than double the pre-H1N1 level.

58. However, some critical care experts have expressed the view that as conventional ventilation therapies and technologies for the treatment of ARDS develop and improve, there will be a reduction of demand for ECMO. The treatment of ARDS continues to receive interest from research groups across the world. The Group is aware that there are trials which have finished recruiting or that are currently recruiting that have/are examining different and novel therapies in the treatment of this condition.

59. The Group acknowledges that the results of these trials will influence and may alter how clinicians treat patients with ARDS and those of the trials that produce positive results will contribute to the clinicians’ armamentarium to treat ARDS. As the evidence base for treatment of ARDS changes so will the referral pattern and demand for ECMO. These novel therapies will sit alongside ECMO in the treatment of ARDS and cannot alter the recommendations of the Group at this time.
60. Views of Intensive Care experts in Scotland suggest that future demand for ECMO will continue to be relatively small.

Quantitative Assessment of Need for ECMO therapy in Scotland

61. The Group felt that the most appropriate approach to this difficult issue was through a needs assessment. In a needs-based health service, supply of services to the population should in principle be determined by profiles of need, but in practice, it is often easier to assess rates of supply. Information about population need may be inferred from comparison of supply rates in different populations.

62. In this assessment of need for adult ECMO services, a comparative method was chosen after initial investigation of several other possible approaches. The full report is available in Appendix 11. The basis of the comparative approach is comparison of the levels of the same service in different populations.

63. Information about rates of supply per million of the adult population is shown in Table 1 and reflects figures for activity prior to the H1N1 pandemic. The numbers and rates shown in the table should be considered provisional for a number of reasons, most of which reflect the highly specialised and geographically concentrated nature of the service.

64. In particular, the undernoted factors should be taken into account when considering the figures in table 1:

- In some cases, there may be some uncertainty about the denominator.
- The numbers shown are crude rates only. The demand for ECMO will be affected by demographic differences in catchment populations, but no account has been taken of these factors in the information shown.
- The use of crude rates may obscure real differences in supply between catchment populations. These differences might become evident if the rates were standardised.
- The numerator may in some cases include patients transferred to the centre from areas outside the normal catchment area.
- The numbers treated are very small compared with the size of the denominator. For this reason, a small difference in numbers treated could make a considerable difference to the rates shown.
- Adult and paediatric patients may be defined differently at different centres.
- The estimated demand at some centres may include some cardiac patients.
- Differences in supply rates may also reflect differences between centres in referral criteria, differences in mode or retrieval and differences in medical behaviour.
- The figures were collected over different time periods.
### Table 1: Numbers of treatments and rates of supply for adult respiratory ECMO services

<table>
<thead>
<tr>
<th>Centre</th>
<th>Annual number of patients treated</th>
<th>Population (millions)</th>
<th>Need (per million, per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbourne</td>
<td>5</td>
<td>4</td>
<td>1.25</td>
</tr>
<tr>
<td>Ireland</td>
<td>6</td>
<td>3.5</td>
<td>1.71</td>
</tr>
<tr>
<td>Sweden</td>
<td>19</td>
<td>9</td>
<td>2.11</td>
</tr>
<tr>
<td>Leicester</td>
<td>50</td>
<td>60</td>
<td>0.83</td>
</tr>
<tr>
<td>Sydney</td>
<td>10</td>
<td>6</td>
<td>1.67</td>
</tr>
<tr>
<td>Queensland</td>
<td>10</td>
<td>5</td>
<td>2.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td><strong>87.5</strong></td>
<td><strong>1.14</strong></td>
</tr>
</tbody>
</table>

65. Even with the above qualifications, certain broad conclusions may be drawn from the information about supply rates shown in Table 1. These are:

- The overall rate of supply from all centres combined was 1.14 cases per million per year.
- The greatest supply rate was for the Swedish centre at 2.1 per million population, and the smallest, for the Centre in Melbourne at 1.2 per million per year.
- The variation in rate per million was relatively small, although small differences in rates expressed per million correspond to considerable numbers of patients treated.
- The relatively small amount of variation suggests that most population need is currently met.
- Larger variations would have suggested the presence of significant amounts of unmet need in populations with lower supply rates.

### Projected requirements

66. Requirements for an adult respiratory ECMO service in Scotland have been estimated by assuming four different levels of supply. These are described in Table 2 as Scenarios 1 to 4. The levels of supply were chosen to reflect broadly the range of values shown in the table and were respectively 1, 1.5, 2, and 2.5 cases per million per year. The predicted requirements for each of these options have been calculated by applying each rate to the Scottish population represented by the Mid Year Estimate for 2008. The predictions are shown in Table 2.
Table 2: Estimated numbers of ECMO treatments required in adults aged more than 19 years

<table>
<thead>
<tr>
<th>NHS Board</th>
<th>Population</th>
<th>Scenario 1 (1 per million per population)</th>
<th>Scenario 2 (1.5 per million per population)</th>
<th>Scenario 3 (2 per million per population)</th>
<th>Scenario 4 (2.5 per million per population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayrshire &amp; Arran</td>
<td>283,601</td>
<td>0.4</td>
<td>0.6</td>
<td>0.7</td>
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67. It is a function of any health service to plan for potential demand for a particular service. It is imperative that a respiratory ECMO service should be able to handle a minimum level of demand, but also to have the capacity to cope with the fluctuations in demand that the Group has been advised should be expected, and which are likely to be heightened in the post-H1N1/ CESAR trial environment.

68. Of each of the scenarios, it is most likely that potential demand in Scotland for adult respiratory ECMO will be comparable to that in scenario 4, which most closely represents the demand experienced by the Swedish centre.

69. The Swedish centre is in effect the nearest comparable model for Scotland. Sweden is geographically similar to Scotland, with the majority of its population concentrated in one geographical area but with a requirement to provide access for populations in more peripheral areas as well. It is also the most established service, reflecting the demand that a mature service can expect. Though Leicester is recognised as the UK’s nationally commissioned respiratory ECMO service, its participation in the CESAR trial required that the number of patients it has treated
has been determined by selection criteria and the requirements of the trial rather than a reflection of the actual demand or need of the UK population for adult respiratory ECMO.

70. It is also likely that demand in future will increase, because of the role of ECMO during the H1N1 pandemic and the publicity surrounding it. Clinicians in Australia have indicated that evidence of post-H1N1 figures so far would indicate that levels of demand for this treatment have, on average, doubled.

Conclusion

71. This approach suggests a likely future demand for adult respiratory ECMO of a minimum of between 10 and 12 cases annually for the Scottish population, similar to levels experienced by the Swedish ECMO centre.
CHAPTER 4: PRINCIPLES, REQUIREMENTS AND PROJECTED COSTS OF A RESPIRATORY ECMO SERVICE

72. Chapter 2 concluded that referral to a centre capable of providing adult respiratory ECMO could be clinically effective and may be taken to be cost effective. This was based on results from a hospital recognised as a centre of excellence by ELSO. If a service were in future to be provided in Scotland it should be provided to a similar standard as those services already available to Scottish patients in Leicester and/or Stockholm.

Basic requirements of an adult respiratory ECMO service

Standards and quality assurance

73. The Expert Group endorses the advice from experts, including those in the designated paediatric ECMO centre in Glasgow, that any new service should be part of the ELSO network for quality assurance purposes, and should adhere to its guidelines, a sample of which are included in Appendix 6.

74. Specifically, a centre should provide data on outcomes to the ELSO Registry as a means of benchmarking performance against other units and gaining specific feedback from ELSO for quality improvement purposes. Attendance at ELSO and other peer group meetings also allows for the sharing and discussion of complex or unusual cases, adding to the learning and improvement of clinicians providing ECMO.

75. The Expert Group notes that some clinicians in Australia expressed concerns that the ELSO Registry did not meet their requirements and that they are proposing to develop an Australasian registry. It would be important however for a Scottish unit to work closely with other Northern European units. Therefore, any new unit providing adult respiratory ECMO in Scotland requires to be part of the ELSO network, and to provide a service that complies with its guidelines.

Service design

76. The location and infrastructure of any new unit is key to its ability to provide a high quality service. Experts have recommended that ECMO should not be seen as a stand-alone service but rather is one of a range of treatments for patients with severe but potentially reversible respiratory failure which are otherwise available in general ICUs. As mentioned in chapter 2, the CESAR trial did not examine the benefit of ECMO, but the benefit of referral to an ECMO capable centre. The centre needs to be capable of supporting all aspects of respiratory failure, and have ready access to other specialist services.

77. The centre in Sweden provides ECMO as a distinct program with its own pool of dedicated staff trained to provide ECMO primarily. This was intended to avoid the tensions which can exist between an ECMO service and the priorities and demands of its main ‘host’ service. Whilst the model appears to work there, the Expert Group recommends that embedding an ECMO service into a wider service is desirable, to enable ‘flexing’ up or down when demand requires.
Where to embed

78. Of the ECMO centres the Group has spoken to, most units were based in general ICUs in acute general hospitals and, with one exception, all were led by experienced and established intensivists. Only Glenfield in Leicester based its unit within a cardiothoracic ICU and was led by a cardiothoracic surgeon, reflecting the historical interest of that particular surgeon in the provision of respiratory ECMO; however this unit is adjacent to a general ICU.

79. The Expert Group supports evidence from the majority of experts that an ECMO service for respiratory failure should be located within an adult general ICU rather than within a cardiothoracic ICU. It was emphasised that ECMO should be considered one of a spectrum of interventions for ARDS. For this reason, an ECMO unit led by clinicians who have credible expertise in the provision of whole-system and non-ECMO respiratory support for these patients would be both clinically appropriate and credible with referring clinicians, who will in general be intensivists.

80. It is also the case that some patients referred for ECMO remain and improve on conventional ventilation, whilst those placed on ECMO who survive require post-ECMO intensive care so any service must be provided by clinicians accustomed to providing a range of conventional ventilation therapies as well as ECMO.

81. Clinicians at Glenfield noted that immense pressure had been placed on the hospital’s ability to provide elective surgery and to act as the regional cardiothoracic centre. This is particularly the case with patients requiring long runs on ECMO, who would represent a greater pressure on cardiac ICU bed capacity as well as compromise capacity for elective surgery.

82. The Expert Group also heard from critical care experts about the need for an ECMO service to be seen as part of a strong critical care network. This view is confirmed in feedback from the Scottish Critical Care Delivery Group. This Group comprising Regional Critical Care Clinical leads across Scotland is of the strong and consistent view that patients on respiratory ECMO require ongoing care from specialist Intensive Care clinicians in addition to on-site specialist ECMO expertise.

83. However, all centres emphasised the importance of having close working relationships with cardiothoracic surgical and perfusionist colleagues and the majority of experts recommended that ECMO should be provided in a hospital with cardiothoracic services onsite, to ensure access to the skills and support of cardiothoracic surgeons and perfusionists.

84. Many of the units which gave advice to the Group are based in hospitals with heart and lung transplant programmes, which often provide cardiac ECMO for support. The Expert Group recognises that this may increase patient numbers but does not consider it essential for the provision of respiratory ECMO. The Group heard that although there were similarities between technologies and expertise necessary to provide respiratory ECMO and mechanical cardiac support, there were also important differences so that the two groups should not be seen as interchangeable.
85. The Expert Group therefore endorses the need for on-site cardiothoracic surgical and perfusionist (but not necessarily transplant) services.

86. In summary, the Expert Group recommends that if a new adult respiratory ECMO service is established, it should be intensivist led, and embedded into a unit already recognised as providing a high standard of advanced respiratory care for patients with ARDS.

Co-location - vital services

87. Experts have advised that it is vital to have access on-site to blood transfusion services. Blood and blood products are required for priming the circuits, for putting a patient onto ECMO and maintaining that patient on ECMO. Though patients requiring respiratory ECMO have less demand for blood and blood products than cardiac patients, the potential for bleeding during treatment remains significant.

88. Other services considered vital onsite include microbiology, biochemistry, haematology, and virology laboratory services; diagnostic imaging and radiology; cardiology; general and vascular surgery; anaesthetics, physiotherapy and dietician services. Some of these services would be provided in a general hospital, but the majority of these services would only be available in larger acute general hospitals. The full list of these services is included in Appendix 4.

89. Experts felt that all of these services must be ready to assist with a patient on ECMO at any time.

Co-location – desirable services

90. Experts consider co-location with a paediatric ECMO unit to be desirable if possible, as this would provide cross-fertilisation between services in terms of skills and volume of cases and would represent the opportunity to ‘pool’ blood and blood related products. Staff in Sweden are trained to treat neonates, paediatrics and adults, but this is unusual.

91. Other services considered desirable but not vital on-site include rehabilitation; neurology; nephrology and maternity. Although renal failure is common, intensivists rather than nephrologists generally lead the treatment of this in ICU. These are also included in Appendix 4.

Staff requirements

92. The Group considers that a dedicated and organised ECMO team is essential. Key themes in the evidence were that the service should be led by a visible and credible Director and have an effective ECMO co-ordinator. Experts have advised that a multidisciplinary team should be in place before a unit begins operating and that in addition to the necessary equipment, protocols and trained staff, institutional commitment from the host hospital and its management is vital.
93. All experts emphasised the importance of ECMO specialist nurses as the main provider of treatment and care for the patient and of the need for staff to be able to respond quickly to challenges. In some units they have also taken on the role of the perfusionist.

94. Experts have advised that staff should have regular refresher training and drills, as well as regular reviews of outcomes, which should be discussed and shared with other ECMO units in the ELSO network.

95. The majority of experts considered the ability to ‘flex’ staff from ICU functions to ECMO functions and back to be the most cost-effective way of providing an ECMO service. Centres in Australia and in Leicester and Yorkhill have general ICU staff that are trained to provide ECMO when it is required. At the majority of centres, input from surgeons is provided on-call, on a rotating basis.

**Retrieval and repatriation**

96. Each of the UK, European and Australian ECMO services consulted had a form of retrieval for patients requiring ECMO and therefore the Group considers that any new unit should also be capable of providing a retrieval service.

97. Different models of retrieval were apparent at the various centres, reflecting different approaches to the issue of retrieving patients who are already on ECMO:

- Glenfield – has trained staff who are available to assess patients on-site before bringing them to Leicester for treatment (though at times of high demand they have had difficulty providing this);
- Karolinska – has trained staff who are available to assess patients on-site either for retrieval to the Karolinska or treatment onsite;
- Melbourne – has trained staff who are available to assess patients on-site and who place the patient on ECMO during transport to back to the unit.
- Sydney – has a state-funded retrieval service whereby staff are available to assess patients on-site and who place the patient on ECMO during transport back to the unit. Assistance is provided by a doctor and a paramedic from the state Medical Retrieval Service too.

98. It has been universally acknowledged that transporting very sick patients is potentially hazardous and requires skilled and trained staff.

99. Experts emphasised that any retrieval service for ECMO presents a number of challenges and requires to be well equipped, organised and experienced, with major organisational and staff input. The importance of good communication between the referring and retrieving teams during any patient transfer, including the dissemination of referral criteria and transfer protocols, has been emphasised as crucial.

100. There were some differences of opinion regarding whether a patient should be transported on ECMO or not. Glenfield clinicians consider that transporting on ECMO may lead to later referrals from units and that the associated pressures and difficulties of retrieving in a limited time frame. In Australia and Sweden, retrieval on
ECMO is common practice, as clinicians consider that there is evidence that patients on ECMO are more stable for transfer compared with those on conventional ventilation and as ECMO technology has adapted to transportation demands. This is heavily influenced by the size and the geography of these countries which require transportation over long distances.

101. The provision of an ECMO retrieval service was not considered by clinicians in Australia to have a major impact on services at the base hospital, which is minimised by having a pool of staff – both ECMO and cardiothoracic – available or on call. However, longer retrievals from remote locations have had an impact on resources to the extent that cardiothoracic surgeons are now considering whether senior trainee staff can be sent on retrievals in their place.

102. Given that the existing units provide a retrieval service, any new service would require to do the same in order to ensure equivalent care. Whether this was provided by the ECMO unit or a separate transport team could be explored, but the Group considers that referring hospitals should not be responsible for transporting this group of patients. The Group recommends that there should be an aspiration to provide transport on ECMO as an option but not necessarily in the first phase of a new programme.

Networking

103. Every centre emphasised the importance of close cooperation with fellow centres as a means of sharing capacity and coping with fluctuations in demand. In addition, centres working within a network can provide a source of advice, support and collaboration. Therefore the Group considers that any new unit should establish close working relationships with centres already participating in a network model.

Costs associated with the provision of adult respiratory ECMO

104. Adult respiratory ECMO is a highly specialised technique demanding even higher levels of medical, nursing and technical/laboratory support than a Level 3 ICU facility, including double the number of nurses per traditional intensive care bed. An ECMO service therefore also has to have access to a large range of skills – including trained intensive care medical and nursing staff with specific expertise in ECMO, perfusionists, respiratory specialists, operating theatre support, laboratory services, physiotherapists and other physicians and surgeons as well as numerous other services.

Projected costs of a new service in Scotland

105. NHS Scotland has experience in the provision of a paediatric ECMO service commissioned through NSD, a full cost breakdown for which is provided in Appendix 8. Based upon this experience, and also reflecting on information gained from looking at service delivery models around the world, the cost of providing the necessary core staff to deliver an adult ECMO service to meet anticipated demand of between 10 and 12 patients per annum would be in the region of £1.5 million to £1.8 million.
Table 3: Projected costs of a new adult respiratory ECMO service in Scotland

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<td>548</td>
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106. It should be noted that whilst this caseload for adults is half that of the paediatric ECMO service, the average number of bed days and resources required and involved are double.

107. In addition, one-off setup costs for ECMO machines would require to be taken into account. Advice from centres currently providing this service and also based upon scope of 10 to 12 cases per annum would indicate that 3 machines would be required, which includes one as a back-up.

108. One-off setup costs for transport and retrieval of £445K also require to be taken into account, based upon two sets of portable devices and also the adaptation of existing transport to enable the equipment to be transported safely. These costs are based upon the experience of the ECMO retrieval service recently set up in New South Wales Australia (provided in Australian dollars at the current exchange rate in Appendix 9). It should also be noted that this model is based upon transfer of patients on ECMO, which is not the practise used by the UK centre at Leicester.

**Likely costs of continuing access to UK service through current reciprocal arrangements**

109. The National Commissioning Group (NCG) is responsible for commissioning nationally designated clinical services which are either very low volume or require rare skills. In some circumstances, the portfolio of NCG services overlaps with Scottish nationally-designated services. Some services for very rare conditions are only available at one or two sites in the UK.

110. NSD makes a contribution towards the cost of Scottish residents accessing these services, although some are funded entirely by NCG on a UK basis. Through these arrangements Scottish patients currently have access to the UK’s national adult respiratory ECMO service in Leicester.

111. Based upon the current contract charges for 2009-10 (as displayed in Appendix 10) the cost of providing adult respiratory ECMO for between 10 and 12 cases per annum to meet the forecast demand for Scotland is between £910K to...
£1,092K. The £46K variable cost per case is in line with the estimated provision of a service in Scotland; however the fixed costs are significantly lower due to UK the unit handling 10 times the volume scoped to meet the Scottish demand.

Conclusion

112. An ECMO service requires to participate in ELSO and to operate in line with its standards (to which Glenfield and the Karolinska centres also adhere), and within a network of centres to share experience and capacity.

113. It should be intensivist-led and embedded in a leading intensive care unit but with cardiothoracic services available on site. It also requires a number of essential services onsite and access to a range of desirable services nearby, consistent with services provided by larger acute general hospitals.

114. The projected cost of establishing a new service in Scotland is between approximately £1.5m and £1.8m per year, with additional one-off set up costs of approximately £445K for machinery and the associated machinery and adaptations for providing transport and retrieval. This is compared with a cost of continuing access to the UK service as it stands at present of between £0.9m and £1.1m per year.
CHAPTER 5: SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Evidence of efficacy and safety

115. The CESAR trial has been reviewed in this report together with other Randomised Controlled Trials (RCTs) and observational trials. A number of limitations have been highlighted. In addition, the question of the precise place of ECMO in relation to the range of alternative treatment strategies available in critical care management remains a matter for debate. However, on balance, the Expert Group believes that ECMO could be efficacious, safe and clinically effective in the treatment of adult patients with potentially reversible advanced respiratory failure.

Cost Effectiveness

116. The Health Technology Assessment was also reviewed. Much of the evidence cited was from the recent CESAR trial. The lifetime predicted incremental costs per QALY were quoted a £19,000 (95% CI 7,622 to 59,200). The CESAR trial investigators acknowledge that their model was based on some highly simplified assumptions and that more robust local models need to be constructed.

117. The Group considers this to be within acceptable levels and therefore that respiratory ECMO for adults may be taken to be cost-effective.

Demand

118. The predicted level of demand is uncertain. This reflects the paucity of robust epidemiological data and uncertainty about future patterns of referral. A comparative needs assessment model was used based on current supply rates. This indicated a potential demand for adult respiratory ECMO in Scotland of around 10 to 12 Scottish cases per year, but this may increase post-H1N1 and with the move to earlier intervention. On the other hand, improvements in conventional ventilation methods may reduce the demand.

Service Model

119. Several experts from across the world gave evidence to the Group. The conclusions for each part of the patient pathway are set out below:

Referral process

- There is a need to develop awareness and relationships with referring clinicians.
- There is debate about referral criteria and the range of conditions which are suitable for ECMO.
- The decision to commence ECMO treatment depends on a range of factors and is often dependent on clinical judgement for each individual case.
- All respondents did, however, agree that patients should have acute but reversible lung insult which may be due to a variety of causes.
Experts advise that there needs to be a committed leader who is both respected within the service and has the confidence of referring clinicians.

Transport

- It was recognised by all respondents that there were significant risks associated with transporting such sick patients.
- There was debate about whether patients were best transferred on ECMO support or on conventional ventilation.
- Some ECMO units transported patients using their own ECMO trained staff, whilst others used specialist transport teams.
- The Expert Group considered that referring hospitals should not be responsible for transporting this group of patients.

Service

- Most services are led by intensivists with support from other specialities, although the UK service has historically been provided by cardiothoracic surgeons.
- There was debate about whether a respiratory ECMO service should be embedded within a general intensive care setting or whether it should be located with cardiac ECMO provision as part of a lung and heart transplant unit.
- The Expert Group considers that respiratory ECMO is one of a range of interventions which intensivists employ in the treatment of adults with Acute Respiratory Distress Syndrome (ARDS) and therefore it is better to treat patients within a general intensive care setting. It recognises the importance of links with cardiothoracic surgery, and the possibility that additional cases from cardiac ECMO may boost the numbers of patients which are treated and enable better use of expertise and resources.
- As these patients are very sick, many of the experts interviewed highlighted a range of services which were considered essential and desirable. Some of these services would be provided in a general hospital, but the majority of these services would only be available in larger acute general hospitals.

Cost

- Adult respiratory ECMO is a highly specialised technique demanding higher levels of medical, nursing and technical laboratory support than a Level 3 ICU facility.
- The cost of establishing a new service in Scotland for between 10 and 12 adult patients per annum would be between approximately £1.5m to £1.8m per year, with additional one-off set up costs of approximately £445k for machinery and the associated machinery and adaptations for providing transport and retrieval.
- This is compared with the current cost of continuing access to the UK service as it stands at present of between £0.9m and £1.1m per year.

Quality

- Recognising that this is small volume service, it is vital that clinical outcomes should be carefully recorded and available for comparison with other units.
• Any Scottish unit should contribute to the international ELSO database to enable international comparisons on outcome.
• All experts supported the concept that any potential new units should work within a UK network and indeed, with colleagues in Sweden, to cope with fluctuations in demand and for the purposes of support, advice and collaboration.
**Recommendations**

1. The Expert Group believes that there is sufficient evidence to support the efficacy, safety and clinical effectiveness of ECMO for adult patients with potentially reversible advanced respiratory failure.

2. Patients from Scotland therefore should have continued access to this treatment.

3. The Group recommends that in order to be clinically effective and safe, any adult respiratory ECMO service requires to treat a minimum of 10 patients a year. It is likely that the potential demand for adult respiratory ECMO in Scotland will be between 10 and 12 patients a year. However there is uncertainty about this figure and future trends.

4. It is therefore feasible to establish an adult respiratory ECMO service in Scotland, which would cost approximately £1.5m to £1.8m per year, with additional one-off set up costs of approximately £445k. However, the alternative is to continue to access facilities provided at a UK level through the nationally commissioned service at Leicester, the cost of which would be between £0.9m and £1.1m per year.

5. An adult respiratory ECMO service requires to be led by a committed intensivist and located within a general intensive care environment capable of providing a range of respiratory interventions and with access to the range of specialties required by critically ill patients.

6. An adult respiratory ECMO service also requires to provide a safe form of assessment and retrieval service which ensures patients can be transported safely. The Group recognises the challenges for a new unit of transporting patients on ECMO but recommends that a service aspires to do this.

7. The Group recommends that a small volume service such as adult respiratory ECMO should be provided to international standards and should participate in a collaborative network with other adult respiratory ECMO centres in order to manage fluctuations in demand and to ensure clinical excellence.
APPENDIX 1: MEMBERSHIP OF THE SCOTTISH ECMO EXPERT GROUP

- Dr Simon Mackenzie (Chair), President, Scottish Intensive Care Society;
- Dr John Colvin, Chair of the Scottish Critical Care Delivery Group;
- Dr Alexander Binning, Clinical Director for Critical Care NHS Greater Glasgow and Clyde;
- Dr Paul Wilson, Clinical Director ICU, Crosshouse Hospital;
- Dr Mike Winter, Medical Director, National Services Division (NSD);
- Dr Stan Murray, Consultant in Public Health Medicine, NHS Greater Glasgow & Clyde;
- Dr Steve Stott, Consultant Anaesthetist, NHS Grampian;
- Peter Croan, Finance Director, NSD;
- Dr Jennifer Armstrong, Senior Medical Officer, SGHD;
- Professor Colin Robertson, Chief Medical Officer Adviser;
- Elizabeth Porterfield, Healthcare Planning Division, SGHD;
- Rebecca Lowe, Healthcare Planning Division, SGHD.
APPENDIX 2: ACKNOWLEDGEMENTS

The Group would like to thank the undernoted individuals and groups for their time and invaluable input to the work of the Group and this Report:

- Mr Richard Firmin, Director of the UK nationally commissioned centre for adult respiratory ECMO; Mr Giles Peek; and Ms Gail Faulker, ECMO Co-ordinator.
- Dr Kenneth Palle Palmer, Director and Ms Inger Mossberg, Head nurse of the ECMO centre in Stockholm.
- Mr Alistair Flowerdew, Medical Director of Golden Jubilee National Hospital, Clydebank.
- Dr Pauline Strachan and Dr David Noble, Deputy Medical Director, NHS Grampian and Clinical Lead for Intensive Care at Aberdeen Royal Infirmary.
- Mr Carl Davis; Mr Jamie Redfern and Dr Andrew Macintyre Consultant Paediatrician, General Manager, and Consultant in Paediatric Intensive Care Medicine, Royal Hospital for Sick Children, Yorkhill Hospital, Glasgow.
- Dr Martin Ashton-Key, Medical Advisor to the UK National Commissioning Group.
- Dr Mo Al-Haddad; Ms Judith Roulston; Dr Mike Fried, Consultant Lead for Glasgow Shock Team; Acting Lead Nurse for Glasgow Shock Team and Consultant in Anaesthesia and Critical Care Medicine.
- Mr Edward Brackenbury, Former ECMO fellow at Glenfield Hospital, Leicester and presently a consultant cardiothoracic surgeon at the Royal Infirmary, Edinburgh.
- Dr David Simpson, Associate Clinical Director of Anaesthesia at Royal Hospital Sick Children, Edinburgh.
- Dr Rachel Green, Clinical Director, West of Scotland Blood Transfusion Service.
- Dr Andrew Davies and Dr Vincent Pellegrino, Deputy Director of ICU at Alfred Hospital, Melbourne, and the lead for its ECMO service.
- Dr Nikki Blackwell, Senior Staff Specialist, ICU at the Prince Charles Hospital, Brisbane.
- Dr Paul Forrest, Head of Cardiothoracic Anaesthesia and Perfusion at the Department of Anaesthetics, Royal Prince Alfred Hospital, Sydney.
- Dr Edmund Carton and Serena O’Brien, Director and ECMO Coordinator of the adult respiratory ECMO program at the Mater Hospital, Dublin.
- Dr Chris Cairns, lead for the Scottish Intensive Care Society’s Evidence Based Medicine Group.
- The Scottish Health Technologies Group of NHS Quality Improvement Scotland.
- The Scottish Critical Care Delivery Group.
- The Scottish Intensive Care Society Audit Group.
# APPENDIX 3: STANDARD EVIDENCE TEMPLATE

## A: REFERRAL

### Referrers

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<td>What does a centre require for you to refer to it?</td>
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</tbody>
</table>

### Providers

<table>
<thead>
<tr>
<th></th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Who is on call to accept the first phone call?</td>
</tr>
<tr>
<td>6.</td>
<td>What information is required to take a decision on treatment?</td>
</tr>
<tr>
<td>7.</td>
<td>Who makes the decision to accept the patient?</td>
</tr>
<tr>
<td>8.</td>
<td>Do you have referral criteria, and if so, what are they?</td>
</tr>
<tr>
<td>9.</td>
<td>Roughly what % of calls would you turn down and why?</td>
</tr>
<tr>
<td>10.</td>
<td>What % of patients transferred for ECMO receive it and what % do you manage conventionally?</td>
</tr>
<tr>
<td>11.</td>
<td>How do you process patients (and paperwork) returning to a referring centre?</td>
</tr>
</tbody>
</table>

## B: RETRIEVAL

### Referrers and Providers

<table>
<thead>
<tr>
<th></th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.</td>
<td>Do you operate transfer (to) or retrieval (returning from) arrangements for referrals to ECMO centres?</td>
</tr>
<tr>
<td>13.</td>
<td>If so, how do these arrangements operate?</td>
</tr>
<tr>
<td></td>
<td>• Ambulance run</td>
</tr>
<tr>
<td></td>
<td>• Staffing</td>
</tr>
<tr>
<td></td>
<td>• Training</td>
</tr>
<tr>
<td></td>
<td>• Rotas etc.</td>
</tr>
<tr>
<td>14.</td>
<td>What is your maximum boundary of retrieval?</td>
</tr>
<tr>
<td>15.</td>
<td>What is the impact on capacity of providing a retrieval service? What is required in terms of staffing, time demands and equipment?</td>
</tr>
<tr>
<td>16.</td>
<td>Do you establish ECMO before transfer, and if so on what criteria?</td>
</tr>
</tbody>
</table>

### Providers

<table>
<thead>
<tr>
<th></th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td>What is the geographical spread of referrals you receive?</td>
</tr>
</tbody>
</table>
### C: TREATMENT

<table>
<thead>
<tr>
<th>Providers</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. What are the accepted indicators for ECMO treatment?</td>
<td></td>
</tr>
<tr>
<td>19. Are these written?</td>
<td></td>
</tr>
<tr>
<td>20. What are they based upon?</td>
<td></td>
</tr>
<tr>
<td>21. Are they breached, and if so, how often and why?</td>
<td></td>
</tr>
<tr>
<td>22. Do you anticipate these changing?</td>
<td></td>
</tr>
<tr>
<td>23. Do you provide ECMO interventions for rescue purposes [or proactively]?</td>
<td></td>
</tr>
<tr>
<td>24. How long do patients spend on ECMO?</td>
<td></td>
</tr>
</tbody>
</table>

### D: SERVICE DESIGN AND INFRASTRUCTURE

<table>
<thead>
<tr>
<th>Providers</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Number of Machines</td>
<td></td>
</tr>
<tr>
<td>26. Number of beds and purpose when not used</td>
<td></td>
</tr>
<tr>
<td>27. What staff make up the multidisciplinary team?</td>
<td></td>
</tr>
<tr>
<td>28. How does the MDT operate?</td>
<td></td>
</tr>
<tr>
<td>29. What are the leadership and reporting arrangements for the team?</td>
<td></td>
</tr>
<tr>
<td>30. What staff training is required to set up a service and what ongoing training is required and received to maintain it?</td>
<td></td>
</tr>
<tr>
<td>31. What do specialist ECMO staff do when not providing ECMO?</td>
<td></td>
</tr>
<tr>
<td>32. What are the step down arrangements when treatment ends?</td>
<td></td>
</tr>
<tr>
<td>33. What are the arrangements for liaising with, involving and supporting family/relatives?</td>
<td></td>
</tr>
<tr>
<td>34. What is service’s adherence to agreed Michigan ECMO standards?</td>
<td></td>
</tr>
<tr>
<td>35. Do you participate/collaborate with other centres in a national or wider</td>
<td></td>
</tr>
</tbody>
</table>
network? If so, how do you work with them and how often?

36. Are you a participant in the emergent UK network (linked to paediatric ECMO network) and providing input into the UK database?

37. What is the base service for your ECMO service?

38. What services are critical and desirable for running the unit, notwithstanding the current H1N1 context?

<table>
<thead>
<tr>
<th>Service</th>
<th>Crucial</th>
<th>Desirable</th>
<th>Not required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric ECMO Unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric ITU/Critical Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternity services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITU/Critical Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology, biochemistry &amp; haematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lab services</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infection control</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diagnostic imaging</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiology</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cardiothoracic surgery</td>
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<td></td>
</tr>
<tr>
<td>General surgery</td>
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<td></td>
<td></td>
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<tr>
<td>Vascular surgery</td>
<td></td>
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<tr>
<td>Cardiovascular perfusion</td>
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<td></td>
<td></td>
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<tr>
<td>Anaesthetics</td>
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<td></td>
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<tr>
<td>Radiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapy/Occupational therapy</td>
<td></td>
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<td></td>
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<tr>
<td>Dietician</td>
<td></td>
<td></td>
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<tr>
<td>Orthopaedics</td>
<td></td>
<td></td>
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<tr>
<td>Rehabilitation</td>
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<td></td>
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<tr>
<td>Neurology</td>
<td></td>
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</tr>
<tr>
<td>Nephrology</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

39. Which of these services are crucial to have onsite?

40. Are there any other services you consider crucial or desirable?

CRUCIAL:

DESIRABLE:

E: OUTCOMES AND PERFORMANCE MANAGEMENT

<table>
<thead>
<tr>
<th>Providers</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>41. How many patients do</td>
<td></td>
</tr>
<tr>
<td>you treat per month/year</td>
<td></td>
</tr>
<tr>
<td>and what is the case mix?</td>
<td></td>
</tr>
<tr>
<td>42. What do you consider</td>
<td></td>
</tr>
<tr>
<td>to be the minimum and</td>
<td></td>
</tr>
<tr>
<td>maximum number of cases</td>
<td></td>
</tr>
<tr>
<td>for a unit to operate</td>
<td></td>
</tr>
<tr>
<td>effectively?</td>
<td></td>
</tr>
<tr>
<td>43. Do you have any</td>
<td></td>
</tr>
<tr>
<td>information/statistics on</td>
<td></td>
</tr>
<tr>
<td>activity and outcomes we</td>
<td></td>
</tr>
<tr>
<td>could have?</td>
<td></td>
</tr>
<tr>
<td>• Numbers of patients</td>
<td></td>
</tr>
<tr>
<td>treated in last 5 years;</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis/ indications</td>
<td></td>
</tr>
<tr>
<td>for support;</td>
<td></td>
</tr>
</tbody>
</table>
- Severity at commencement;
- Complications/ critical incidents;
- Mortality figures

44. Do you have mechanisms in place to discuss and review outcomes?

45. What is the relationship with ELSO? Do you provide information on outcomes to the ELSO Registry?

46. Do you follow up patients after discharge? If so, how and for how long?

### F: DEMAND AND FUTURE PLANNING

<table>
<thead>
<tr>
<th>Providers</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Can you indicate what kind of impact providing the maximum capacity of ECMO available in your service would have on: Beds; Staffing; Other services?</td>
<td></td>
</tr>
<tr>
<td>48. What do you consider to be the demand for respiratory ECMO [per million of the population]?</td>
<td></td>
</tr>
<tr>
<td>49. What do you consider to be the future likely demand for respiratory ECMO?</td>
<td></td>
</tr>
<tr>
<td>50. What do you consider to be the minimum and maximum service provision required based on population need, in terms of: Beds; Staffing; Equipment.</td>
<td></td>
</tr>
<tr>
<td>51. Do you have workforce and service planning in place to correspond with this?</td>
<td></td>
</tr>
<tr>
<td>52. What do you consider will be the future shape and activity of your service?</td>
<td></td>
</tr>
</tbody>
</table>

### F: IS THERE ANYTHING WHICH HASN’T BEEN COVERED BUT WHICH YOU FEEL IS IMPORTANT?

### G: COMMENTS
## APPENDIX 4: GROUP AND EXPERT VIEWS ON ESSENTIAL AND DESIRABLE SERVICES

<table>
<thead>
<tr>
<th>Service</th>
<th>Crucial</th>
<th>Desirable</th>
<th>Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric ECMO Unit</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric ITU/Critical Care</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternity Services</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITU/Critical Care</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Committed team with leader and coordinator</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology, biochemistry, haemotology, virology lab services</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic imaging</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventional Radiology</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic surgery</td>
<td>E, G</td>
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</tr>
<tr>
<td>General surgery</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular perfusion</td>
<td>E, G</td>
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</tr>
<tr>
<td>Anaesthetics</td>
<td>E, G</td>
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<tr>
<td>Physiotherapy</td>
<td>E, G</td>
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<tr>
<td>Dietician</td>
<td>E, G</td>
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<tr>
<td>Occupational Therapy</td>
<td>E, G</td>
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<tr>
<td>Orthopaedics</td>
<td>G</td>
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<td>E</td>
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<tr>
<td>Rehabilitation</td>
<td>E, G</td>
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<tr>
<td>Neurology</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrology</td>
<td>E, G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart &amp; Lung Transplantation/Bridge to Transplant program</td>
<td>E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social work/support services for family and relatives</td>
<td>E</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G  Views of the Group

E  Views of the Experts
APPENDIX 5: SAMPLE ECMO INDICATIONS/ CONTRA INDICATIONS

Taken from Adult Respiratory ECMO Policy and Guidelines Protocol developed by the Royal Prince Alfred and Liverpool Public Hospital Intensive Care Units, New South Wales

Indications for ECMO

ECMO is indicated for potentially reversible, life-threatening forms of respiratory and/or cardiac failure, which are unresponsive to conventional therapy and it is always applied at the discretion of the managing intensivist or cardiac surgeon. It is also occasionally used in patients with irreversible cardiac or respiratory disease in patients who are candidates for a heart or lung transplant.

Selecting the form of ECMO

1. **V-A ECMO**: applied for the management of cardio-respiratory failure or cardiac failure where use of a ventricular assist device (VAD) is deemed inappropriate.
   - **Central V-A ECMO**: In cases where V-A ECMO is required for cardiac support and where lung function is poor (large shunt) peripheral V-A ECMO should be avoided. This is because any native cardiac output present will deliver hypoxic blood from the pulmonary veins preferentially to the cerebral circulation (potentially causing severe cerebral hypoxia). Central V-A ECMO is most often employed in patients undergoing cardiac surgery.
   - **Peripheral V-A ECMO** is appropriate when reasonable lung function exists and cardiac surgery is not required

2. **Low-flow V-A ECMO (ECMO-CPR)** is used only for initial support and stabilisation in emergent conditions requiring V-A support

3. **V-V ECMO** is used for isolated respiratory failure when adequate heart function for the duration of ECMO is anticipated

4. **Hi-flow V-V ECMO** is used when circuit flow via a single access cannula is inadequate to maintain safe oxygenation. This may be required if smaller access cannulae have been placed percutaneously (although 25FR percutaneous cannulae have recently become available), in which case a second venous access cannula may be required (eg. from an internal jugular vein).

Pathological Processes Requiring V-A ECMO

**Common**
1. Graft failure: post heart / heart-lung transplant
2. Cardiogenic shock: AMI and complications (including: wall rupture, papillary muscle rupture, refractory VT / VF)
3. Post cardiac surgery: unable to wean safely from cardiopulmonary bypass using conventional supports
4. Sepsis with profound cardiac depression
5. Drug overdose with profound cardiac depression

**Other**
1. Myocarditis
2. Chronic cardiomyopathy: as a “bridge” to longer term ventricular assist device
3. Pulmonary embolism
4. Cardiac or major vessel trauma
5. Massive haemoptysis / pulmonary haemorrhage
6. Pulmonary trauma
7. Acute anaphylaxis
Pathological Processes Requiring V-V ECMO

Common
1. Severe pneumonia
2. ARDS
3. Acute lung (graft) failure following transplant
4. Pulmonary contusion

Other
1. Alveolar proteinosis
2. Smoke inhalation
3. Status asthmaticus
4. Airway obstruction
5. Aspiration syndromes
APPENDIX 6: ELSO GUIDELINES FOR ECMO CENTRES

PURPOSE

These guidelines developed by the Extracorporeal Life Support Organization, outline the ideal institutional requirements needed for effective use of extracorporeal membrane oxygenation (ECMO). The Extracorporeal Life Support Organization recognizes that differences in regional and institutional regulations especially concerning hospital policies may result in variations from these guidelines. These guidelines will be reviewed and updated every three years in an attempt to keep the document current.

INFORMATION AND BACKGROUND

Extracorporeal Membrane Oxygenation (ECMO) was first used successfully for neonates with respiratory failure in 1975. Today it is an accepted treatment modality for neonatal, pediatric and adult patients with respiratory and/or cardiac failure failing to respond to maximal medical therapy. ECMO is defined as the use of a cardiopulmonary bypass circuit for temporary life support for patients with potentially reversible cardiac and/or respiratory failure. ECMO provides a mechanism for gas exchange as well as cardiac support thereby allowing for recovery from existing lung and/or cardiac disease. It has been estimated that approximately 2800 newborns could benefit could benefit from ECMO annually in the US (one of every 1309 live births). Pediatric and adult patients are being successfully treated in increasing numbers.

GENERAL

A. ECMO centers should be located in tertiary centers with a tertiary level Neonatal Intensive Care Unit, Pediatric Intensive Care Unit and/or Adult Intensive Care Unit.

B. ECMO Centers should be located in geographic areas that can support a minimum of 6 ECMO patients per center per year. The cost effectiveness of providing fewer than 6 cases per year combined with the loss, or lack of clinical expertise associated with treating fewer than this number of patients per year should be taken into account when developing a new program.

C. ECMO Centers should be actively involved in the Extracorporeal Life Support Organization (ELSO) including participation in the Central Registry.

ORGANIZATION

A. General Structure:

The ECMO center should be located in a tertiary level intensive care unit with the following components.

- There should be a physician ECMO program director with responsibility for the overall operation of the center.
- There should be an ECMO coordinator with responsibility for the supervision and training of the technical staff, maintenance of equipment, and collection of patient data.
- The multi-disciplinary ECMO Team should have quality assurance review procedures in place for annual ECMO evaluation internally.
- Formal Policy and Procedures outlining the indications and contraindications for ECMO, clinical management of the ECMO patient, maintenance of equipment, termination of ECMO therapy, and follow-up of the ECMO patient should be available for review.
- Appropriate laboratory space for training and continuing medical education should be available.

B. Staffing Issues:

The ECMO staff should meet the requirements of their subspecialty training as set forth by their specific governing board (American Board of Surgery, American Board of Pediatrics, etc.). In addition, ECMO staff should meet the training requirements described below.
1. The medical director should be either a board certified neonatologist, a board certified critical-care specialist, or a board certified pediatric, cardiovascular, or thoracic surgeon.

2. The ECMO coordinator may be an experienced neonatal, pediatric, or adult intensive care registered nurse or registered respiratory therapist with a strong ICU background (minimum of 1 year of ICU experience), or a certified clinical perfusionist with ECMO experience.

3. An ECMO-trained physician will provide 24-hour on-call coverage for the ECMO patient. The physician may be a neonatologist, pediatric or adult criticalcare specialist, a neonatology or critical care fellow, or other physician who has completed at least three years of post-graduate pediatric, surgical, or adult medical training and has specific ECMO training.

4. There shall be an ECMO clinical specialist as described below to provide 1:1 or 1:2 care throughout the course of ECMO.

5. The ECMO Specialist should have a strong intensive care background (1 year of NICU or PICU experience preferred) and have attained one of the following:
   - Successful completion of an approved school of nursing and achievement of a passing score on the state written exam given by the Board of Nursing for that state; OR
   - Successful completion of an accredited school of respiratory therapy and have successfully completed the registry examination for advanced level practitioners and be recognized as a Registered Respiratory Therapist (RRT) by the National Board of Respiratory Care (NBRC). OR
   - Successful completion of an accredited school of perfusion and national certification through the American Board of Cardiovascular Perfusion (ABCP). OR
   - Physicians trained in ECMO who have successfully completed institutional training requirements for the clinical specialists.

6. In addition to #5, it is recommended that a bedside pediatric or NICU nurse provide 1:1, or 1:2, care throughout the course of ECMO.

7. Additional support personnel from the permanent hospital staff should be available on a 24 hour/day on-call basis:
   a. Physicians or other medical personnel who routinely care for neonates from the following disciplines:
      - Pediatric/adult cardiology
      - Pediatric/adult cardiovascular surgery
      - Pediatric/general surgery
      - Cardiovascular perfusion
      - Pediatric/adult anesthesiology
      - Pediatric/adult neurosurgery
      - Pediatric/general radiology
      - Genetics
   b. Biomedical engineer
   c. Respiratory therapists experienced in intensive care

8. The following consultants should be available as needed.
   - Pediatric/adult neurology
   - Pediatric/adult nephrology
   - Occupational/physical therapist
   - Developmental/rehabilitation specialist

9. A fully trained and equipped transport team should be available 24 hours a day.

10. Trained individuals capable of providing development follow-up or rehabilitation should be available and capable of providing long-term follow-up to the ECMO patient.
C. Physical Facilities and Equipment

11. If the space allocated for ECMO is located outside the ICU, it should be in close proximity to and have appropriate communication with the ICU to assure additional staff support for any emergency that may arise.

12. An ECMO system consists of a suitable blood pump, a system for servoregulation to balance venous drainage rate from the patient and blood return to the patient, an appropriate blood heat exchanger and warming unit, appropriate disposable materials including membrane oxygenator tubing packs, and connectors, all suitable for prolonged extracorporeal support.

13. A device for monitoring the level of anticoagulation (ACT or other) with appropriate supplies should be at the bedside.

14. The following equipment should be readily available:
   a. Backup components of the ECMO system and supplies for all circuit components.
   b. Adequate lighting to support surgical interventions.
   c. Surgical instrument set for revision of cannulae or exploration for bleeding complications.

15. The following support facilities with staff should be available on a 24-hour basis.
   a. A blood gas laboratory
   b. Laboratory for blood chemistry and hematologic testing
   c. Blood bank
   d. Radiographic support including cranial ultrasound and CATscan
   e. Cardiovascular operating room facilities with cardiopulmonary bypass capabilities located within the hospital doing ECMO and available 24 hours a day.

D. Staff Training and Continuing Education

16. Each ECMO center should have a well-defined program for staff training, certification, and re-certification. This program should include: didactic lectures, laboratory training with the ECMO equipment, bedside training, and a defined system for testing proficiency of the team members (See ELSO Guidelines for Training and Continuing Education of ECMO Specialists)

17. Each member of the ECMO team should successfully complete this program.

18. A well-defined program of routine continuing education and emergency training for ECMO staff should be outlined with records documenting participation by active team members.

19. It is recommended that team members not involved in ECMO pump management for > 3 months should be required to go through a re-certification process as defined by the ECMO program.

E. Selection Criteria

20. ECMO is indicated for selected neonatal, pediatric and adult patients with severe, acute cardiac and/or respiratory failure who have failed to respond to conventional medical management.

21. Each ECMO center should develop institutional criteria for ECMO therapy, including indications and contraindications.

22. It is recommended that the ECMO center develop guidelines for transfer of the ECMO patient.

F. Patient Follow-up

23. Each ECMO center should have a well-defined developmental follow-up program for the ECMO patient with appropriate subspecialty support (refer to ELSO Guidelines for Follow-up).
G. Program Evaluation

24. A well-defined system should be instituted for assuring that formal meetings of key ECMO team members occurs on a routine basis to review cases, equipment needs, administrative needs, and other pertinent issues. Minutes to these meetings should be available for review.

25. A prompt review of any major complication or death should be held both with ECMO team members and with the responsible Morbidity and Mortality committee in the hospital. These reviews should be conducted under the relevant quality assurance laws for the state where the center is located.

26. Formal clinical-pathological case reviews with a multi-disciplinary approach should be regularly conducted (as outlined by JCAHO regulations).

27. An Annual Data Report, utilizing the center's collated data, or the collated report of data submitted to the ELSO Neonatal ECMO Registry, should be available for quality assurance review.

28. Records documenting maintenance of equipment should be kept (as per JCAHO regulations).
APPENDIX 7: NHS QUALITY IMPROVEMENT SCOTLAND (NHS QIS): REVIEW OF EVIDENCE BASE FOR ADULT RESPIRATORY ECMO

Health technology description

Extracorporeal membrane oxygenation (ECMO) technology provides temporary life support to patients with severe life threatening but potentially reversible cardiac or respiratory failure. It may also be used to assist in the transition from cardiopulmonary bypass to ventilation after heart surgery. ECMO is a form of extracorporeal life support (ECLS). These terms are commonly used interchangeably, although this is not strictly accurate: ECMO specifically describes the process of oxygenating the blood outside the body. It involves removing blood from the patient’s venous circulation and passing it through an external membrane lung where oxygen is added and CO2 is removed before it is returned to the patient’s circulation. The ECMO circuit comprises access cannulae, connecting tubing, blood pump, membrane lung, heat exchanger and monitoring devices. To reduce the risk of blood clotting, an anticoagulant, usually heparin, is given intravenously and the circuit itself may be heparin-bonded. ECMO used purely for respiratory support is usually provided in the veno-venous mode whereby blood is removed from and returned to the venous circulation via percutaneous cannulation while the patient’s own cardiac output continues to sustain the systemic circulation. When ECMO is used to provide respiratory support mechanical ventilator settings can be lowered, thereby allowing the patient’s lungs to ‘rest’ and reducing the risk of lung injury associated with high pressure and high oxygen ventilation. ECMO can be continued for several days or weeks until the patient’s lung function improves. ECMO patients require continual monitoring by a trained ECMO specialist in addition to conventional intensive care nursing.

Respiratory support ECMO for adults in Scotland is currently provided at Aberdeen Royal Infirmary and available through the UK national ECMO centre at Glenfield Hospital in Leicester and the accredited European centre at the Karolinska Hospital in Stockholm.

Clinical indications

In adults the most common application of ECMO is to provide respiratory support to patients with acute severe reversible respiratory failure who have a poor chance of survival despite optimal conventional intensive care. The commonest causes of respiratory failure that lead to a requirement for ECMO are hypoxemic (low arterial blood oxygen) acute respiratory distress syndrome (ARDS) of various aetiologies and other causes of diffuse pneumonitis. The technique has recently come to the fore in the management of patients who develop ARDS following infection with the pandemic influenza A(H1N1) virus (‘swine flu’). Other respiratory applications include status asthmaticus and severe acute reactive airways disease. Patients are selected for ECMO on the basis of the severity of respiratory failure and mortality prediction rather than aetiology.

While most ARDS deaths are caused by multiple organ system failure around 20-40% are attributable to acute respiratory failure.1 It has been estimated that as many as 350 adults each year in the UK may have severe but potentially reversible acute respiratory failure.2 About 30 adult survivors after ARDS and ECMO are reported annually to the international ELSO registry.3 With regard to influenza A(H1N1) infection specifically, investigators in Australia and New Zealand reported 2.6 ECMO cases per million inhabitants during the southern hemisphere winter (June to August) of 2009.4

Clinical effectiveness

Methods

Studies for this review were identified from a literature search on ECMO for respiratory distress conducted by the Scottish Government Department of Health (SGDH), and supplementary searches undertaken by Quality Improvement Scotland. The supplementary searching entailed modifying the SGDH by adding additional relevant search terms, updating the existing searches and searching additional sources. The databases searched were CDSR, DARE, HTA, CENTRAL, EMBASE, MEDLINE, MEDLINE In-Process, and Web of Knowledge. These sources were searched to November 2009. One researcher selected studies for inclusion. Additional sources of information were obtained from personal contacts.
Randomised controlled trials

CESAR trial (HTA report)
The clinical effectiveness of ECMO in adults with severe respiratory failure has been evaluated in a randomised controlled trial (RCT) conducted by the UK national ECMO centre at Glenfield Hospital in Leicester. This multicentre pragmatic trial (CESAR) randomised 180 adults to receive either conventional ventilatory support or transfer to the specialist centre for consideration for ECMO. The trial recruited patients with potentially reversible respiratory failure (Murray score ≥3 or uncompensated hypercapnoea with pH <7.2). Exclusion criteria included high pressure or high FiO2 ventilation for more than 7 days, and contraindications to heparinisation or continued active treatment. Patients randomised to consideration for ECMO who were either haemodynamically unstable or stable but unresponsive to the centre’s standard ARDS respiratory intensive care protocol within 12 hours received veno-venous ECMO via percutaneous cannulation and lung protective ventilation according to the centre’s protocol for management on ECMO. ECMO was not instated during transfer to the specialist centre. Patients in the control group received conventional management at their treating tertiary ICU (some requiring transfer from referring hospitals). Although the units providing conventional management were advised on best practice the control treatment was not standardised across centres due to lack of agreement on protocolised care. The primary outcome was death or severe disability at 6 months follow-up and the trial was powered to detect reduction by a third in the rate of this composite outcome. The primary analysis was described as intention-to-treat however it is more accurate to describe it as an available case analysis because it did not include patients lost to follow up.

Sixty-eight of the 90 patients allocated to consideration for ECMO actually received ECMO treatment: three patients died before transfer, two died in transit and 17 responded to conventional intensive care at the specialist centre. The primary analysis (which excluded three control group patients with incomplete follow-up information) showed a statistically significant reduction in the risk of death or severe disability at 6 months in favour of referral for ECMO (33/90 ECMO versus 46/87 Control; RR 0.69, 95% CI 0.05, 0.97, p=0.03). This equates to an absolute survival benefit without severe disability of 16% (95% CI 1.7, 30.7) and a number needed to treat of 6 (95% CI 3, 59). Fewer patients died in the ECMO group (33/90) than in the control group (45/90) but the difference was not statistically significant (RR 0.73, 95% CI 0.52, 1.03, p=0.07). Overall only one patient (in the control group) was known to have severe disability at 6 months.

Patients referred for ECMO had a longer median length of stay in ICU (24 days, IQR 13, 40.5) and in hospital (35 days, IQR 15.6, 74) compared to the control group (13 days, IQR 11, 16 and 17 days, IQR 4.8, 45.3, respectively). The median duration of ECMO was 9 days (IQR 4.0, 7.1). A significantly higher proportion of patients referred for ECMO received a low volume ventilation strategy compared to those allocated to conventional care (93% versus 70%, p<0.0001) and the duration of low volume ventilation was significantly longer (23.9 days, sd 20.4 versus 15 days, sd 21.1, p<0.0001). A significantly higher proportion of patients in the group referred for ECMO received steroids (84% versus 64%, p=0.001) and molecular albumin recirculating system (MARS) liver support (15 versus 0, p<0.0001) while there was no difference in the use of other ancillary treatments. There was no statistically significant difference between the groups in the use of high-frequency, oscillation or jet ventilation, nitric oxide, prone positioning, or any measure of health status at 6 months follow-up. The trial investigators consider long-term follow-up of the trial participants (initially at 10 years) to be a future research priority.

In terms of internal validity the CESAR trial was well-conducted. Central randomisation protected against selection bias and minimisation (weighted randomisation) was used appropriately to balance the treatment groups by entry hospital, primary diagnosis, age, organ failure, duration of prior ventilation, and mode of trial entry (hypoxic or hypercarbic). The assessment of outcomes at 6 months follow-up was blinded to treatment allocation. Although the primary outcome was a composite of death or severe disability all but one of the outcome events were deaths. The primary analysis compared conventional care with referral for consideration of ECMO, and not ECMO treatment per se, which was appropriate to the design of the trial. The primary analysis did show a statistically

1 95% CIs for absolute risk reduction and NNT calculated by QIS
significant benefit in favour of ECMO referral over conventional care, however missing data for three control group patients with incomplete follow-up could be sufficient to change the findings. In a sensitivity analysis the difference in the primary outcome effect between ECMO referral and conventional care was no longer statistically significant if the three patients with incomplete follow-up were assumed not to have severe disability (p=0.051). Of the patients allocated to consideration for ECMO the rate of survival was the same among those who went on to receive ECMO treatment (43/68) and those who did not (14/22).

With regard to the applicability of the findings, the CESAR trial evaluated a single tertiary centre treatment package (including availability of ECMO, steroids and MARS machine) with non-standardised management of ADRS. The outcomes achieved at the national ECMO specialist centre may not be generalisable to other hospitals with ECMO capability and the lack of standardisation in control group management is a potential source of bias. In the CESAR trial conventional care was provided at 43 different hospitals. The trial investigators acknowledged that the outcomes in the control group might have been better if conventional management had been more controlled or provided in a specialist centre. However, they believe that the outcome in the control arm of the trial should accurately reflect the prognosis for adults with severe respiratory failure in the majority of ICUs in the UK. Implying possible benefit from ECMO to patients in Scotland will require consideration of whether the control group management in the CESAR trial adequately reflects routine management of ARDS in Scottish general units. Details of actual management received in each group after randomisation are tabulated in the HTA report (Chapter 3, Table 4, p18). Three of the trial’s recruiting centres were in Scotland (Ayr, Ninewells and Raigmore Hospitals), which together recruited 8 patients (the recruitment period was July 2001 to August 2006).

Previous RCTs
Two earlier RCTs (published in 1979 and 1994) have been summarised in a systematic review of ECMO in adults with ARDS that was undertaken prior to the publication of the CESAR trial. The earliest trial compared conventional mechanical ventilation (with unrestricted peak airway pressures) with ventilation supplemented with partial veno-arterial ECMO in 90 adults with acute respiratory failure. The second trial compared low-frequency positive pressure ventilation and extracorporeal carbon dioxide removal (ECCO₂R, i.e. CO₂ removal accomplished by the ECMO circuit and oxygenation by ventilation) with protocol-driven mechanical ventilation in 40 adults with ADRS. Both trials showed no significant improvement in survival with ECMO (9.3% versus 8.3%, and 33% versus 42%, respectively), both reported a high incidence of bleeding and both were stopped early. Meta-analysis using a Bayesian random effects model to accommodate heterogeneity showed no significant difference in the odds of mortality between ECMO and control (OR 1.28, 95% credible interval 0.24, 6.55). The generalisability of the findings from these early trials to modern ECMO is limited due to substantial differences in case selection, ventilation strategies, ECMO circuit design, disease management and clinical expertise in the use of ECMO technology.

Non-randomised studies
The systematic review by Chalwin et al also identified three non-randomised prospective studies (published between 1997 and 2006) and 35 case series (published between 1976 and 2007). The non-randomised studies reported poorer survival outcomes in ECMO patients (53% to 55%) compared to non-ECMO patients (61% to 89%). The case series reported survival to discharge rates ranging from 10% to 100% (median 53%). In the largest series comprising 255 adult patients treated at the University of Michigan medical centre between 1989 and 2004 the survival to discharge rate was 52%. As of May 2008 the international ECLS Organisation Registry had collated data on 972 adults who received ECMO support for respiratory failure of whom 53% survived to hospital discharge.

Investigators in Australia and New Zealand have reported an inception cohort study describing all admissions to the 187 ICUs in those countries due to infection with influenza A(H1N1) during the southern hemisphere winter (June to August) of 2009 and a case series describing 68 patients treated with ECMO for influenza-associated severe ARDS. In the cohort, a total of 722 patients with confirmed A(H1N1) infection were admitted to ICUs (28.7 cases per million inhabitants, 95% CI 26.5, 30.8) of whom 92.7% were under the age of 65 years and 9.1% were pregnant women. Adults aged 25 to 49 years accounted for the highest number of admissions. The total number of ICU bed days was 8815 and the maximum daily occupancy 7.4 beds per million inhabitants (95% CI 6.3, 8.5). Out of 706 patients for whom data were available 456 underwent mechanical ventilation for a median duration of 8 days (IQR 4, 16). Fifty-three patients were subsequently treated with ECMO (2.1 per
The Australia New Zealand case series reported on all 68 patients with severe ARDS who received ECMO in 15 ICUs (of whom three were children <15 years of age). The patients included 53 A(H1N1) confirmed cases (as reported in the inception cohort) and 15 suspected cases (8 with serological evidence of influenza A infection that was not sub-typed and 7 with preceding symptoms of unconfirmed influenza-like illness). This was equivalent to an incidence rate of 2.6 ECMO cases per million inhabitants. The median duration of ECMO was 10 days (range 7, 15). Based on all 194 patients with either confirmed A(H1N1) or serological evidence of influenza A infection, who required mechanical ventilation in these ICUs, the duration of mechanical ventilation was significantly longer among the 61 patients who received ECMO compared to the 133 treated without ECMO (median 18 days, IQR 19, 27 versus 8 days, IQR 4, 14, p=0.001). The length of stay in ICU was also significantly longer (median 22 days, IQR 13, 32 versus 12 days IQR 7, 18, p=0.001) and the ICU mortality rate significantly higher (23% versus 9%, p=0.01). At the time of reporting 14 of the total 68 ECMO patients had died (21%, 95% CI 11%, 30%), 6 remained in ICU of whom 2 were still receiving ECMO, 48 had survived to ICU discharge (71%, 95% CI 60%, 82%) of whom 32 survived to hospital discharge and 16 remained as inpatients.

Mikkelsen et al conducted a retrospective cohort study of ECMO in adult respiratory failure due to status asthmaticus using ECLS Organisation Registry data. Between 1986 and 2006 data were available for 24 status asthmaticus ECMO patients and 1233 who received ECMO for respiratory failure due to other causes. Survival to hospital discharge was significantly higher among the asthmatics (83.3% status asthmaticus versus 50.8% other causes; OR 4.86, 95% CI 1.65, 14.31, p=0.004) and remained so after adjustment for potential confounders. The same pattern was observed in the more recent data collected between 1997 and 2006 (92.8% versus 51%). Whether ECMO confers a survival advantage over other salvage treatment options for this indication remains unknown.

There are few data on long-term outcomes following ECMO for respiratory failure in adults. Investigators in Stockholm recently published a follow-up study of 21 adult survivors who received ECMO for severe ARDS at the European accredited ECMO centre at the Karolinska Hospital. The median time from ECMO discharge to follow-up was 26 months (range 12, 50). The majority of patients had persistent minor lung function abnormalities and limited residual changes in lung parenchyma. Most patients reported a reduction in health-related quality of life due to breathing problems although the majority (76%) had returned to their former occupation. The aforementioned University of Michigan case series also reported that almost all of the adult ARDS survivors treated between 1989 and 2004 returned to normal functioning by one-year after hospital discharge albeit with a slightly restricted pulmonary functioning pattern. These studies do not provide information about long-term outcomes among patients who receive conventional care.

Safety
ECMO complications are mainly those associated with cannulation, anticoagulation and circuit disruptions. Risks to the patient include perforation of blood vessels during cannulation, bleeding, heparin-induced thrombocytopenia, infection and haemolysis. The relevance of data on the incidence of complications in studies undertaken before and during the 1990s (including the early RCTs) is probably limited. Developments in ECMO technology over time have reduced the risk of mechanical complications. Features such as roller pumps used with a servo-regulator minimise haemolysis, polymethylpentene membrane lungs prevent plasma leakage, and heparin bonded-circuits reduce the level of systemic anticoagulation needed. Due to its complexity and potential complications once ECMO has been initiated patient management requires continual monitoring by a trained ECMO specialist in addition to the usual nursing care provider. Furthermore, it is now argued that ECMO should only be provided in specialist centres even though transporting critically ill patients to a specialist centre for treatment is in itself hazardous. In the CESAR trial one participant suffered fatal vessel perforation during percutaneous cannulation and two died in transit to the specialist centre, one from catastrophic pulmonary haemorrhage and the other due to the failure of the oxygen

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2 This author uses the term ECLS to mean ECMO (M Mikkelsen, Personal Communication)
supply in the ambulance. There is some evidence from retrospective observational studies that inter-hospital transfer on mobile ECMO systems may improve survival.

**Economic implications**

The CESAR trial investigators evaluated whether ECMO for severe adult respiratory failure was cost-effective and used decision modelling to estimate the utility gain over a predicted lifetime. The additional average health care cost per patient referred for ECMO was more than double the average cost of conventional management. Patients allocated to consideration for ECMO incurred average total costs of £73,979 compared to £33,435 for conventional management, a difference of £40,544 (95% CI 24,799 to 56,288) (UK prices, 2005). The additional cost to the NHS of a policy of providing access to the ECMO service was estimated at £4,828,320 per annum for 120 patients and £14,082,600 for 350 patients. The incremental cost-effectiveness ratio (ICER) of referral for ECMO compared to conventional care was £250,162 per additional survivor without severe disability at 6 months based on costs incurred during the trial, and £128,621 based on costs estimated from non-case-mix adjusted NHS tariffs. Referral for ECMO resulted in a gain of 0.03 (95% CI 0.00 to 0.06) QALYs at 6 months follow-up giving a cost per additional QALY of £1,631,124. The lifetime predicted incremental cost per QALY was £19,000 (95% CI 7622 to 59, 200) at a discount rate of 3.5%. The investigators recommended that local economic models need to be developed to assess cost-effectiveness in different contexts and that further research is needed to develop robust models that take account of geographical location (including costs of transport), economies of scale and long-term quality of life.

No other economic evaluations of ECMO respiratory support in adults were identified.

**Concluding comments**

Apart from the CESAR trial and two earlier RCTs, and excluding individual case reports, the evidence for ECMO respiratory support in adults comprises mainly observational data from cohorts and case series. The CESAR trial is the best conducted trial to date in terms of minimising bias, and the only RCT that is relevant to current practice. The investigators acknowledged the trial’s limitations, particularly the unavoidable variation in control group management. However, cautious interpretation of the ‘survival without severe disability' benefit shown in favour of ECMO is warranted because of the potential for missing data on disability from a very small number of patients to change the findings. The trial was not designed to compare ECMO treatment outcomes with conventional management. Policy makers need to consider the applicability of the trial intervention scenario—referral for consideration of ECMO—to what actually happens in clinical practice. Non-randomised studies, on average, report ECMO survival rates around 50%. These studies, particularly case series, are more susceptible to bias than RCTs, which limits the extent to which inferences can be made about treatment effects. The ECMO case series identified for this review did not have matched usual care comparator groups. The Australia New Zealand influenza investigators pointed out that registry data from previous winters were not directly comparable to their winter 2009 inception cohort data. Also, the outcome data from those studies (cohort and ECMO case series) were censored at the time of reporting. With regard to cost, the CESAR trial investigators stressed that their economic model was based on some highly simplified assumptions and that robust local cost-effectiveness models need to be constructed.

**References**


APPENDIX 8: PAEDIATRIC ECMO COST PROFILE 2008/9

### Paediatric ECMO Cost Profile 2008/09

<table>
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<th>Variance</th>
<th>Projected outturn</th>
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**Summary**

- Fixed Costs 1,210,472
- Variable Costs (26 Cases) 591,784
- Total Owed By NSD 1,802,256

Less
- Variable Non Contract (1 Cases) 49,478
- Fixed Costs (1 Cases) 50,436
- Total Owed By NSD 1,702,342
# APPENDIX 9: COSTS OF ECMO RETRIEVAL SERVICE IN NEW SOUTH WALES

**BUDGET PROPOSAL TO ESTABLISH AN ECMO RETRIEVAL SERVICE IN NEW SOUTH WALES**

*Establishment Costs: (based on two ECMO retrieval hospitals)*

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<td>14,000</td>
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<td>Brackets for mounting ECMO equipment for transport*</td>
<td>5,000</td>
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<td>Portable blood gas / ACT analyser*</td>
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<td>Portable ECMO heater unit*</td>
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<td>Ultrasonic flow probe</td>
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<td>Development cost: OH and S compliant equipment restraints for helicopter*</td>
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*Exchange Rate as at 10 December 2009 £1 GBP = $1.77 Aus Dollars*
### APPENDIX 10: COSTS OF ADULT ECMO SERVICE AT LEICESTER IN 2009/10

**Costs of Adult ECMO Service at Leicester in 2009/10**

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Capacity increase from 1st August

- Infrastructure/staffing (8 months) £885,119
- Marginal rate (£45,525) £1,365,750

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Capacity increase as of 1st October

- Infrastructure/staffing (6 months) £655,815
- Marginal rate (£45,525) £910,500

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<tr>
<th>Contract as of 1st October 2009</th>
<th>Contract Value</th>
<th>Number of Cases</th>
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</table>

**Adult ECMO Marginal Costs per patient**

- Consultant cost per case payments £560
- Medics - Retrievals £392
- Nursing - Retrievals £392

**Pay Marginal costs**

- Drugs £6,766
- M&S consumables - needles/syringes etc £5,826
- M&S consumables - Ecmo Circuits £10,672
- M&S consumables - Oscillators £3,045
- Haemoscope Thrombelastograph Haemostasis £1,653
- C V V H £1,828

**Medical & Surgical Consumables**

- Transport Costs (22% of all adult patients) £2,975
- PMT Lung Function Tests £162
- Recharges - Blood Products £6,563
- Other Pathology tests £2,957
- Cardiac Investigations £115
- Other Imaging scans £1,026

**Other Support function marginal costs**

- £13,798

**Accommodation charges**

- £593

**Total Marginal Cost**

- £45,525
APPENDIX 11: QUANTITATIVE ASSESSMENT OF NEED FOR ECMO THERAPY IN SCOTLAND

Quantitative assessment of need is a fundamental aspect of population-based planning of health services. An overall assessment of need in its most comprehensive sense should include several different analyses, including an epidemiological determination of need, comparison of service levels in different areas and projection of future requirements for services. In practice, comprehensive assessments of this kind are often not carried out because of considerations of costs or time and the entire needs assessment may comprise only one of these types of analysis. Most Needs Assessments consist of one of the following types:

**Epidemiological assessment:** In an epidemiological needs assessment, the assessment is usually based on particular conditions or diagnoses. This represents population needs assessment in its most pristine form. The starting point would be the incidence and prevalence of relevant conditions in the population of interest, in the context of ECMO services, the incidence of Adult Respiratory Distress Syndrome. The incidence of ARDS would be translated into relevant service indicators, for example, admissions to ITU, beds-days spent in ITU and ECMO treatment. The epidemiological approach to determining need for ECMO could be pursued in principle by using studies of ARDS in the literature or by use of Scottish data for admission to ITU.

**Comparative assessment:** Most needs assessment exercises carried out in practice consist of comparative assessments. In a comparative assessment, no attempt is made to determine a population indicator of need. The assessment consists solely of comparisons of supply rates with the implicit assumption of equal need is each population studies. Comparative assessments are common in the Needs Assessment literature because they can usually be carried out relatively rapidly and because data about supply are usually available.

**Approaches used in this needs assessment:** In this assessment of need for adult ECMO services, each of four different possible approaches has been pursued as far as possible. The use of multiple methods of needs assessment was considered to be justified in view of the perceived lack of information about population need.

The first approach was comparative. The other three approaches, each broadly epidemiological in type, were based on estimates of incidence of Acute Respiratory Distress Syndrome from the literature, analysis of data collected in the SICSAG audit of Intensive Therapy services and estimates of need for ECMO available in the literature. These approaches are considered in greater detail in the following sections. The methodological advantages and shortcomings of each approach are summarised in Table 1.

**Method 1 Comparison of current rates of supply:** In a needs-based health service, supply of services to the population should be determined by profiles of need. In practice, assessment of population need may present considerable methodological difficulty. It is often relatively easy to assess rates of supply, and information about population need may be inferred from comparison of supply rates in different populations. This is the basis of the comparative approach to needs assessment in general in which the level of a service in any population is assessed by comparison with that in another population, for example, the national population, of with some generally accepted population norm or standard.

Information about rates of supply per million adult population is shown in Table. The numbers and rates shown in the table should be considered provisional for a number of reasons, most of which reflect the highly specialised and geographically concentrated nature of the service.

- In some cases, there may be some uncertainty about the denominator
- The numbers shown are crude rates only. The demand for ECMO will be affected by demographic differences in catchment populations, but no account has been taken of these factors in the information shown.
- The use of crude rates may obscure real differences in supply between catchment populations. These differences might become evident if the rates were standardised.
- The numerator may in some cases include patients transferred to the centre from areas outside the normal catchment area.
- The numbers treated are very small compared with the size of the denominator. For this reason, a small difference in numbers treated could make a considerable difference to the rates shown.
- Adult and paediatric patients may be defined differently at different centres.
- The estimated demand at some centres may include some cardiac patients.
- Differences in supply rates may also reflect differences between centres in referral criteria, differences in mode or retrieval and differences in medical behaviour.

Even with these qualifications, certain broad conclusions may be drawn from the information about supply rates shown in Table, as follows:

- The overall rate of supply from all centres combined was 1.14 cases per million per year.
- The greatest supply rate was for the Swedish centre, 2.1 per million population, and the smallest, for the Centre in Melbourne, 1.2 per million.
- The variation in rate per million was relatively small, although small differences in rates expressed per million correspond to considerable numbers of patients treated.
- The relatively small amount of variation suggests that most population need is currently met.
- Larger variations would have suggested the presence of significant amounts of unmet need in populations with lower supply rates.

**Method 2 Incidence of Acute Respiratory Distress Syndrome in adults:** In a needs-based health service, supply of services to the population should be determined by profiles of need, usually represented by incidence and prevalence in the population studies. A summary of some epidemiological studies of incidence is shown in Table. The table shows that there is considerable variation in the reported incidence of ARDS. The estimates vary from 0.587 cases per 100,000 in one study in the US to values of 3.5-5.0 per 100,000 that have been found in several studies. The variation in incidence is partly due to differing criteria for defining ARDS. If the incidence were assumed to be about 5 cases per 100,000 per year in Scotland, then about 200 cases would be expected annually in Scotland, but only a small proportion of these patients would be candidates for ECMO.

In most studies, the definition of ARDS includes reference to the AECC criterion of arterial partial pressure of oxygen to inspired oxygen fraction (p/f) ratio less than 200. The p/f ratio in patients who would be candidates for ECMO is usually considered to be less than 65, but in the absence of more detailed information about the distribution of p/f ratios in critically ill patients, it is not possible to derive a requirement for ECMO therapy from this source.

**Method 3 Norms for provision of ECMO available in literature:** Very few assessments of need have been published for adult respiratory ECMO therapy. The only published guidance appears to be the recommendation given by the ANZ ECMO investigators for requirements related to H1N1 flu. According to these investigators, the incidence of ARDS sufficient to warrant consideration of ECMO therapy exceeds 2.6 per million population.

**Method 4 Analysis of Scottish Intensive Care Clinical Audit Group (SIC SAG) data:** Most patients referred for possible ECMO therapy will already have been in ITU for a variable period. These patients should have reversible respiratory illness, no contraindications to therapy and should have a high probability of mortality in the ITU. In principle, the small fraction of patients who might be candidates for ECMO therapy could be selected using appropriate criteria from a dataset representing all admissions to ITU. In Scotland, data are collected about all admissions to general adult ITUs by the Scottish Intensive Care Clinical Audit Group (SICSAG). An abstract of data for the last five years was made available to the Expert Group for possible use for this purpose.

There is anecdotal evidence that many clinicians use (p/f) ratio to select patients who might benefit from ECMO therapy. For this reason, a derived field for p/f ratio was calculated using the fields for...
arterial partial pressure of oxygen and inspired oxygen fraction. Using this field, the following analyses were carried out:

- Different thresholds of (p/f) ratio were selected
- The mortality in ITU was compared in the groups of patients with (p/f) values respectively above and below the thresholds, and an odds ratio for mortality calculated;
- Predicted referral rates for ECMO therapy were calculated for each threshold

The results of this analysis are shown in Table 4. The main features of the results are as follows:

- Threshold values of the (p/f) ratio between 180 and 40 were tested.
- The odds ratio for mortality increased from 2.99 to 6 as the threshold value declined. This means that patients with (p/f) ratios less than 180 were about three times more likely to die in the ITU than patients with ratios above 180. Patients with (p/f) ratios less than 40 were about six times more likely to die in the ITU than patients with ratios above 40.
- The sensitivity or true positive ratio declined from 88.1% to 1.9% as the threshold fell from 180 to 40.
- The specificity or true negative ratio increased from 24.6% to 99.7% as the threshold fell from 180 to 40.
- The predicted referral rate per million for ECMO therapy fell from 621 to 6 as the threshold fell from 180 to 40.

In summary, the use of (p/f) thresholds appears to be unsatisfactory as a method of predicting requirements for ECMO therapy. This may be shown by considering the prediction for a (p/f) value of 65, a value that is often considered to correspond clinically to severe ARDS. At this level of (p/f) ratio, the following predictions were made:

- Patients with (p/f) values less than 65 were between 3 and 4 times more likely to succumb in ITU
- The sensitivity was 22.9%. This means that only 22.9% of patients who succumbed in ITU would be identified,
- The specificity was 92.2%. This means that 99.7% of patients who would survive would be identified.
- The predicted referral rate would be 95 patients per million.

Summary of methods: The outcomes of the four methods may be summarised as follows:

- **Method 1 Comparison of current rates of supply:** This method suggested a requirement of 1-2 cases per million per year.
- **Method 2 Incidence of Acute Respiratory Distress Syndrome in adults:** This method did not give a direct estimate of need for ECMO therapy.
- **Method 3 Norms for provision of ECMO available in literature:** No information was available except an estimate of 2.6 per million for H1N1 related illness.
- **Method 4 Analysis of Scottish Intensive Care Clinical Audit Group (SIC SAG) data:** This method did not yield realistic estimates of requirement.

In summary, only the comparative method, Method 1, yielded a usable estimate of need for adult respiratory ECMO of 1-2 patients per million per year. For this reason, the requirement for the different health board areas in Scotland has been calculated on a population basis for several supply scenarios:

Scenario 1: 1 case per million per year
Scenario 2: 1.5 cases per million per year
Scenario 3: 2 cases per million per year
Scenario 4: 2.5 cases per million per year
The predicted requirements for ECMO for each of these scenarios are shown in Table 5.

Table 1: Methodological considerations for techniques of needs assessment for adult respiratory ECMO services

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of supply rates</td>
<td>• Relative simplicity of method</td>
<td>• Supply rates are centre orientated not population orientated</td>
</tr>
<tr>
<td></td>
<td>• Information about supply usually available</td>
<td>• May be difficult to attribute treatments to particular Health Boards of Residence or even nationally</td>
</tr>
<tr>
<td></td>
<td>• Most pragmatic approach</td>
<td>• Absolute level of population need not known</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Supply rates may reflect different levels of unmet need or unnecessary interventions</td>
</tr>
<tr>
<td>Use of the incidence of Acute Respiratory Distress Syndrome</td>
<td>• Epidemiologically pristine method</td>
<td>• Differences in definition of ARDS</td>
</tr>
<tr>
<td></td>
<td>• Use of indicator of population need to determine level of service</td>
<td>• Differences in estimation of incidence ARDS</td>
</tr>
<tr>
<td></td>
<td>• Estimates of incidence available</td>
<td>• Difficult to translate estimate of incidence into requirement for interventions because of uncertainty about treatment thresholds</td>
</tr>
<tr>
<td>Analysis of SICSAG data</td>
<td>• Data about admissions to ITU routinely available</td>
<td>• Uncertainty regarding thresholds for ECMO</td>
</tr>
<tr>
<td></td>
<td>• Pragmatic approach</td>
<td>• Data about admissions to ITU routinely available</td>
</tr>
<tr>
<td></td>
<td>• Mortality field allows modelling approach and definition of high risk groups in ITU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Allows comparison of different sets of criteria for ECMO</td>
<td></td>
</tr>
<tr>
<td>Use of estimates of need for ECMO available in the literature</td>
<td>• Epidemiologically sound approach</td>
<td>• No usable estimates of population need available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Numbers of treatments and rates of supply for adult respiratory ECMO services

<table>
<thead>
<tr>
<th>Centre</th>
<th>Annual number of patients treated</th>
<th>Population (millions)</th>
<th>Need (per million, per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbourne</td>
<td>5</td>
<td>4</td>
<td>1.25</td>
</tr>
<tr>
<td>Ireland</td>
<td>6</td>
<td>3.5</td>
<td>1.71</td>
</tr>
<tr>
<td>Sweden</td>
<td>19</td>
<td>9</td>
<td>2.11</td>
</tr>
<tr>
<td>Leicester</td>
<td>50</td>
<td>60</td>
<td>0.83</td>
</tr>
<tr>
<td>Sydney</td>
<td>10</td>
<td>6</td>
<td>1.67</td>
</tr>
<tr>
<td>Queensland</td>
<td>10</td>
<td>5</td>
<td>2.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td><strong>87.5</strong></td>
<td><strong>1.14</strong></td>
</tr>
</tbody>
</table>
### Table 3: Summary of estimates of incidence of Acute Lung Injury and ARDS from published studies

<table>
<thead>
<tr>
<th>Area</th>
<th>Epidemiology of ARDS</th>
<th>Crude Incidence ALI</th>
<th>Crude Incidence ARDS</th>
<th>Author/study</th>
<th>Definition</th>
<th>Catchment Population</th>
</tr>
</thead>
</table>
| US              | 1999-2000  
≥ 15 years | 78.9 per 100,000 per year | 58.7 per 100,000 per year | Rubenfeld et al (1994) | ?????????     | 1.74 million         |
| Scotland        | May-Dec 1999  
> 15 years | 16 per 100,000 per year | 4.5 per 100,000  
3.5 per 100,000  
4.9 per 100,000 | Hughes et al  
Webster et al.  
Villar et al.  
Valta et al. | 3,701,000     |
| Berlin          | 1991  
Adults (in ITU) | 88.6 per 100,000 | 8.3 per 100,000 | Lewandowski et al |           |
| Utah, USA       | 1995 | 8.3 per 100,000 | Thomsen et al, 1995 |     |           |
| Scandavia       | 1997  
> 14 years | 17.9 per 100,000 | 13.5 per 100,000 | Luhr et al 1999  
AECC criteria | 11.74 million |
| Australia       | 1999 | 28 per 100,000 | Bersten et al.  
AECC criteria |     |           | 2.94 million         |

### Table 4: Predicted requirements for ECMO for different thresholds of (p/f) ratio

<table>
<thead>
<tr>
<th>Threshold</th>
<th>OR</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Referrals</th>
<th>Referral rate (per million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>2.99</td>
<td>88.1</td>
<td>24.6</td>
<td>29995</td>
<td>621</td>
</tr>
<tr>
<td>160</td>
<td>2.91</td>
<td>83.7</td>
<td>31.3</td>
<td>27332</td>
<td>566</td>
</tr>
<tr>
<td>140</td>
<td>2.95</td>
<td>77.7</td>
<td>40.1</td>
<td>23813</td>
<td>493</td>
</tr>
<tr>
<td>120</td>
<td>2.99</td>
<td>69.7</td>
<td>50.1</td>
<td>19847</td>
<td>411</td>
</tr>
<tr>
<td>100</td>
<td>2.97</td>
<td>59</td>
<td>60.8</td>
<td>15579</td>
<td>323</td>
</tr>
<tr>
<td>65</td>
<td>3.51</td>
<td>22.9</td>
<td>92.2</td>
<td>4584</td>
<td>95</td>
</tr>
<tr>
<td>50</td>
<td>4.23</td>
<td>7.1</td>
<td>98.2</td>
<td>1221</td>
<td>25</td>
</tr>
<tr>
<td>45</td>
<td>4.68</td>
<td>3.6</td>
<td>99.2</td>
<td>586</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>6</td>
<td>1.9</td>
<td>99.7</td>
<td>290</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 5: Estimated numbers of ECMO treatments required in adults more than 19 years

<table>
<thead>
<tr>
<th>NHS Board</th>
<th>Population</th>
<th>Estimated number of cases annually</th>
<th>Option1</th>
<th>Option 2</th>
<th>Option 3</th>
<th>Option 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayrshire &amp; Arran</td>
<td>283,601</td>
<td></td>
<td>0.4</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Borders</td>
<td>86,992</td>
<td></td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Dumfries &amp; Galloway</td>
<td>116,480</td>
<td></td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Fife</td>
<td>277,813</td>
<td></td>
<td>0.3</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Forth Valley</td>
<td>219,958</td>
<td></td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Grampian</td>
<td>417,648</td>
<td></td>
<td>0.4</td>
<td>0.8</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Greater Glasgow &amp; Clyde</td>
<td>923,468</td>
<td></td>
<td>0.9</td>
<td>1.8</td>
<td>2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Highland</td>
<td>241,123</td>
<td></td>
<td>0.2</td>
<td>0.5</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lanarkshire</td>
<td>425,588</td>
<td></td>
<td>0.4</td>
<td>0.8</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Lothian</td>
<td>637,387</td>
<td></td>
<td>0.6</td>
<td>1.2</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Orkney</td>
<td>15,405</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Shetland</td>
<td>16,581</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Tayside</td>
<td>308,359</td>
<td></td>
<td>0.3</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Western Isles</td>
<td>20,456</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Total</td>
<td>3,990,859</td>
<td></td>
<td>4.0</td>
<td>7.8</td>
<td>10.3</td>
<td>12.9</td>
</tr>
</tbody>
</table>
APPENDIX 12: CRITICALLY APPRAISED TOPIC: ECMO FOR SEVERE RESPIRATORY FAILURE (DR CHRIS CAIRNS, SCOTTISH INTENSIVE CARE SOCIETY’S EVIDENCE BASED MEDICINE GROUP)

ECMO for severe respiratory failure

Management of severe respiratory failure in a specialist centre which is capable of delivering a complex “bundle” of care including a strict ARDS protocol, ECMO, MARS and steroids may improve outcomes when compared with uncontrolled conventional care.


Lead author: Mr Giles J Peek, Department of Cardiothoracic Surgery and Extracorporeal Membrane Oxygenation, Glenfield Hospital, Leicester LE3 9QP, UK. giles.peek@uhl-tr.nhs.uk

Three-part Clinical Question:

1. Patients - aged 18–65 years with severe but potentially reversible respiratory failure.
2. Intervention - comparison of conventional management by intermittent positive-pressure ventilation or high frequency oscillatory ventilation or both against consideration for treatment by extracorporeal membrane oxygenation (ECMO).
3. Outcomes - primary outcome of death or severe disability at 6 months after randomisation. Secondary outcomes were duration of ventilation; use of high-frequency oscillation, or jet ventilation; use of nitric oxide; prone positioning; use of steroids; duration of stay in intensive care; and duration of hospital stay. Health status at 6 months after randomisation was assessed from activities of daily living, quality of life, respiratory symptoms, cognitive psychological state, and lung function.

Search Terms: ARDS, ALI, therapy, respiratory failure, ECMO

The Study: Non-blinded, randomised, controlled trial with intention-to-treat.

The Study Patients: Eligible patients were aged 18–65 years with severe but potentially reversible respiratory failure, and a Murray score of 3 or higher or uncompensated hypercapnoea with a pH of less than 7·20 despite optimum conventional treatment.

Control group (N = 90; 87 analysed): Patients randomly allocated to receive conventional management were given the best critical care practice available in their conventional treatment centre. As a pragmatic trial, a specific management protocol was not mandated, but treatment centres were advised to follow a low-volume/low-pressure ventilation strategy.

Experimental group (N = 90; 90 analysed): Patients randomly allocated to consideration for treatment by ECMO were transferred to Glenfield Hospital. If patients were haemodynamically stable, a standard acute respiratory distress syndrome treatment protocol was used:
  - Pressure-restricted mechanical ventilation at 30 cm H2O
- Positive end expiratory pressure titrated to optimum SaO₂
- FiO₂ titrated to maintain SaO₂ at more than 90%
- Diuresis to dry weight
- Target packed cell volume of 40%
- Prone positioning
- Full nutrition.

If the patient did not respond to this protocol within 12 hours or was haemodynamically unstable, they received cannulation and ECMO. Lung rest settings were peak inspiratory pressure 20–25, positive endexpiratory pressure 10–15, rate 10, and FiO₂ 0·3. ECMO was continued until lung recovery, or until apparently irreversible multiorgan failure.

The Evidence:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time to Outcome</th>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or severe disability</td>
<td>6 months</td>
<td>0.511</td>
<td>0.367</td>
<td>28%</td>
<td>0.144</td>
<td>7</td>
</tr>
<tr>
<td>95% Confidence Intervals:</td>
<td></td>
<td>0% to 56%</td>
<td>0.001 to 0.287</td>
<td>3 to 1867</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6 months</td>
<td>0.500</td>
<td>0.367</td>
<td>27%</td>
<td>0.133</td>
<td>ns</td>
</tr>
<tr>
<td>95% Confidence Intervals:</td>
<td></td>
<td>-2% to 55%</td>
<td>-0.010 to 0.276</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>6 months</td>
<td>0.011</td>
<td>0</td>
<td>100%</td>
<td>0.011</td>
<td>ns</td>
</tr>
<tr>
<td>95% Confidence Intervals:</td>
<td></td>
<td>-0.011 to 0.033</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Event Outcomes</th>
<th>Time to outcome/s</th>
<th>Control group</th>
<th>Experimental group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>6 months</td>
<td>58 (64%)</td>
<td>76 (84%)</td>
<td>0.001</td>
</tr>
<tr>
<td>MARS</td>
<td>6 months</td>
<td>0</td>
<td>15 (17%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Only 68 of the 90 patients in the intervention group received ECMO. 3 died prior to transfer. 2 died in transit. 17 responded to the 12hr ARDS protocol (14 of these survived).
- 43 of the 68 ECMO patients survived.
- Removal of the survivor with severe disability from the analysis would render the benefit non-significant.

EBM Questions:

1. **Do the methods allow accurate testing of the hypothesis?** **No.** This is a multi-centre randomised controlled trial looking at real end points. However one has to be very careful in interpreting the results. This study does not demonstrate a benefit of ECMO alone over optimum conventional therapy. It demonstrates a benefit of specialist centre care (which included the use of a tightly controlled ARDS 12hr protocol and access to ECMO, MARS and steroids) over non-standardised care at other centres. The study would have been methodologically more robust if there had been uniform management of the control group. It would have been interesting to see the results of all patients being subjected to the 12hr ARDS protocol used in the intervention arm given that 82% of responders survived. These were all patients which had “failed” to respond to non-ECMO strategies in the referring centres.
2. Do the statistical tests correctly test the results to allow differentiation of statistically significant tests? Yes.

3. Are the conclusions valid in light of the results? Yes - if conclusion is that study shows a significant improvement in survival without severe disability at 6 months in patients transferred to a specialist centre for a bundle of care including consideration for ECMO.

4. Did any results get omitted and why? Yes - no data available on severe disability for 3 patients in control group.

5. Did they suggest further areas of research? No – but state that “if cannulation at the referring hospital and mobile ECMO support could be used for such patients survival rates might be further improved”.

6. Did they make any recommendations based on the results and were they appropriate? Yes

a. “We are confident that ECMO is a clinically effective treatment for ARDS” – This is probably oversimplistic. Perhaps more accurately, a bundle of care which includes consideration for ECMO is a clinically effective treatment for ARDS.

b. “We recommend further careful modelling of the most cost-effective solution for different settings”

7. Is the study relevant to my clinical practice? Perhaps. Without more detail concerning the management (compliance with ARDSnet recommendations, proning rates, HFOV rates etc) of patients in the control arm it is difficult to judge the applicability of the study to current practice.

8. What level of evidence does the study represent?
   a. ECMO vs conventional management. 1 (RCT with a high risk of bias)
   b. Specialist care bundle including the availability of ECMO vs uncontrolled conventional management. 1* (RCT with a low risk of bias)

9. What grade of recommendation can I make on this result alone? none.

10. What grade of recommendation can I make when this study is considered along with other available evidence? none

11. Should I change my practice because of these results? If patients have failed “best standard care” similar to that delivered in the 12hr pre-ECMO protocol then ECMO could be considered. Clearly the variable use of other therapies (HFOV, APRV ventilation, NO, proning) will lead to variation in referral thresholds.

12. Should I audit my current practice because of these results? Yes

a. Do you follow good practice for ventilation in ARDS?
b. How frequently do you use ‘rescue’ techniques?
c. What is your ARDS mortality?

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