Institution: University of Leicester

Unit of Assessment: UoA2 Public Health, Health Services and Primary Care

Title of case study: Extracorporeal membrane oxygenation (ECMO) in newborn babies: from pioneering technique to accepted practice

1.Summary of the impact

Neonatal extracorporeal membrane oxygenation (ECMO) is a complex procedure of life support used in severe but potentially reversible respiratory failure in newborn infants. In 1993 researchers in Leicester carried out the first and, to date, only large-scale randomised trial comparing the value of ECMO with other means of life support. The trial, with follow-up research at 4 and 7-year intervals, has shown ECMO to be a life-saving and cost-effective treatment, and has led to the establishment of a centrally funded neonatal programme that is estimated to have saved around 340 lives in the UK alone. In 2013 the University remains internationally renowned in the field of ECMO research, and since 2009 Glenfield Hospital has been home to the world's largest ECMO centre for the treatment of newborns, older babies and adults. The trial is still held up by advocates of fair clinical trials as an example of how evidence should translate into practice and policy.

2. Underpinning research

Background

ECMO uses an artificial lung to oxygenate the blood outside the body when a patient has a serious condition which prevents the lungs or heart from working normally. ECMO provides time for the heart to rest and recover, while maintaining a good blood supply to the brain and other organs. First used in the US in the late 1970s, it was still a pioneering technique when Richard Firmin, a paediatric surgeon at Glenfield Hospital in Leicester and an honorary senior lecturer at the University, convinced that the treatment was effective (unlike many other surgeons), approached the children's charity Heart Link for funds to support the introduction of an ECMO programme in Leicester. After a successful series of cases, Firmin and colleagues, buoyed by huge public support and the backing of Leicester MP Greville Janner, persuaded the Department of Health to fund a grant proposal; that was followed by £1.4 million to conduct a randomised controlled trial to assess the effectiveness of ECMO against conventional ventilation.

The randomised controlled trial

The trial was not an easy undertaking. It was complex and expensive. It was ethically and practically difficult to design, given the type of patient being studied: babies with only a 20% chance of survival were assigned randomly to the ECMO group or control group within hours of their birth. At the time ECMO was a highly controversial procedure and the long-term outcomes were completely unknown: there was a very real possibility that reduced mortality might be achieved only with an increase in severe disability among survivors.

Between January 1993 and November 1995, 185 infants with severe respiratory failure were recruited for the study: 93 infants were randomly allocated to the ECMO group and 92 to the conventional treatment group. The trial was led by Professor David Field, who set up the trial, established a protocol and trained staff from five regional centres that formed the UK Collaborative – Leicester, Glasgow, Newcastle, Kings College London and Great Ormond Street Hospital. All five centres recruited babies to the trial. Analysis of results was carried out by the National Perinatal Epidemiology Unit (NPEU) in Oxford.

Recruitment to the trial was stopped two months early by the independent Data Monitoring Committee when the results showed that ECMO had a clear advantage: 63 of 93 infants allocated ECMO survived compared with 38 of 92 allocated conventional care. The conclusion was that ECMO support should be actively considered for neonates with severe but potentially reversible respiratory failure. The results were published in The Lancet by the UK Collaborative ECMO trial Group, with Field listed as corresponding author. Despite the highly specialised nature of the subject matter, the article has been cited 337 times (**1**).

Follow-up research
The UK Collaborative carried out three follow-up studies. Initial assessment at one year showed that the results were in accord with earlier preliminary findings: that ECMO support reduces the risk of death without a concomitant rise in severe disability (**2**).

A fuller assessment at 4 years of age, using six clinical areas (cognitive ability, neuromotor skills, general health, behaviour, hearing and vision) demonstrated both an increased number of survivors (62 versus 38) and an increased number of survivors who were free of disability (30 versus 13) in the ECMO group, compared with the conventional treatment group. The results were published in The Lancet and Field was one of the authors (**3**).

Further research at 7 years, when the children were old enough for educational and other longer-term impacts to be assessed, showed that the ECMO technique resulted in 34 (37%) cases of death and severe disability v. 54 (59%) cases in the conventional treatment group. Although both groups had problems, the ECMO group consistently performed better and the authors concluded that the beneficial influence of an ECMO policy is still present at the age of 7 years, and likely to be at age 18. The results were published in Paediatrics and Field was the corresponding author (**4**).

Other research
The establishment of an ECMO centre in Leicester has enabled a series of studies with global significance. In 2004 a multi-centre trial, again led by Field, and assisted by Marie Horan (MD student) focused on the use of hypothermia as a means of protecting brain function in this group of babies. The results made clear that this intervention, used widely in neonatal ECMO centres around the world, was potentially harmful (**5**).

Research has also been conducted on older babies (12 to 15 months) and adults. The 2001-2006 CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) trial involving seriously ill adult patients led by Dr Giles Peek (Hon Senior Lecturer, Cardiac Surgery) and Professor Andrew Wilson (Primary Care) with colleagues from the London School of Hygiene & Tropical Medicine, showed that 63% of patients given ECMO survived to 6 months without disability compared to 47% of those assigned to conventional treatment with a ventilator (**6**).

Key personnel
Leicester: Professor David Field, Neonatal Medicine (1985 – present)
Other institutions: Prof Diana Elbourne; Prof Miranda Mugford; Dr Stavros Petrou (NPEU, Oxford).
Clinical leads: Mr Richard Firmin (Leicester); Dr Duncan McCrae (Great Ormond Street Hospital); Mr Carl Davies and Dr Charlie Skeoch (Glasgow - Royal Hospital for Sick Children); Prof Anne Greenough (Kings College Hospital); and Mr Leslie Hamilton (Newcastle Royal Victoria Infirmary).

3. References to the research

1 UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996; 348:75-82. (Published on behalf of the UK Collaborative ECMO Trial. Corr. author **Field**)

2 UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: Follow up to one year.*Pediatrics* 1998;101:http//www.pediatrics.org.e1

3 Bennett CC. Johnson A. **Field DJ**. Elbourne D. UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. *Lancet*. 357(9262):1094-6, 2001 Apr 7.

4 Helena McNally, Charlotte C. Bennett, Diana Elbourne, **David J. Field**, for the UK Collaborative ECMO Trial Group United Kingdom Collaborative Randomized Trial of Neonatal Extracorporeal Membrane Oxygenation: Follow-up to Age 7 Years. *Pediatrics* 2006;117: e845-e854 (doi:10.1542/peds.2005-1167).

5 **Horan M**, Ichiba S, Firmin R, Killer H, Edwards D, Azzopardi D Hodge R, Kotecha S, **Field D**. A pilot investigation of mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). *Journal of Pediatrics* 2004;144:301-308.

6 **Peek GJ**, Mugford M, Tiruvoipati R, **Wilson A**, Allen E, Thalanany MM, Hibbert, CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009 Oct 17;374(9698):1351-63.

Grants

1992-97 UK Collaborative ECMO Trial £1,400,000.Department of Health Research & Development

2004 Randomised trial of mild hypothermia during newborn ECMO. British Heart Foundation £383,000. (Plus pilot investigation £77,000 and 2008 supplementary award £41,613)

4. Details of the impact

The trial has had a number of important outcomes: not only did it lead to the establishment of a centrally funded national ECMO service and an international centre for research and training in Leicester, but it also served as an early template for evidence-based research still relevant in 2013.

Setting up of a national ECMO service

The findings of the UK Collaborative trial informed the National Specialised Commissioning Team's (NSCT) Service Standards for the Neonatal Respiratory ECMO Service (designated in 1997, extended in 2005 to include children up to age 18) and the centrally ring-fenced funding of a national neonatal ECMO service based in Leicester, Newcastle, London (Great Ormond Street Hospital) and Glasgow. Service standards and funding are reviewed annually by commissioners and providers. The latest standards refer to 2012/13 (**A**), and the budget for Leicester for this period is just over £4.3 million.

NSCT and providers have a commitment to working together to continually improve the service and react to innovative and dynamic ideas, such as developing a mobile ECMO service for neonatals and children in 2011/12. This is now offered by Glenfield Hospital (**B**).

The response to the CESAR trial has been to commission an adult ECMO service: since 2011 this has operated in five centres, with transport of patients on ECMO as part of the contract (**C**). Glenfield is the only one offering a neonatal, paediatric and adult service.

Quality of life

The neonatal trial provided clear data of improved survival, reduced risk of disability and cost effectiveness. These data remain unchallenged in 2013.

Survival rates: The most immediate impact has been on survival of babies entered into the ECMO programme. Statistically, for every three babies with breathing problems and lung failure treated with ECMO rather than conventional ventilation, one more survived. The number of additional survivors to 2013 can be estimated, based on 100 suitable cases per year in the UK, at 340. Paediatric and adult patients are also being successfully treated in increasing numbers.

Reduced risk of disability: In the neonatal trial, overall rates of impairment and disability were approximately half that seen in survivors treated conventionally. An important feature of both neonatal and adult trials was that the end-point was not survival; it was *intact* survival after an interval. In the case of the neonatal trial it was 1-, 4- and 7-year intact survival based on neurological assessments. In the case of CESAR it was functional independence six months after treatment. An often unrecognised aspect of ECMO support is that the quality of both neonatal and adult survivors is excellent and there is limited long-term functional disability. Provided they are otherwise healthy before needing ECMO, they go on to have long and productive lives in society (**D**).

Cost-effectiveness: In the period from discharge from initial hospitalisation until 7-year follow-up, there was consistently higher use of health care resources in the ECMO arm, but this is largely

because of increased survival in this group. Economic evaluations of ECMO after 4 and 7 years provided rigorous evidence of the cost-effectiveness of ECMO. The measures of benefit used were the life-years gained and the disability-free life-years gained (**E**).

International renown

Since 2009, Leicester has been the largest centre in the world in terms of the combined number of neonatal, paediatric and adult cases annually. The trial data have influenced practice in Europe (Sweden, the Netherlands, France and Germany) and further afield (US and Australia), and many practitioners have come to Leicester to train in the use of ECMO. Glenfield has a reciprocal agreement with European centres, particularly the Karolinska Institute in Stockholm. During the H1N1 influenza A pandemic (swine flu) in 2009/10, which produced a number of young adults whose respiratory function was severely compromised, Glenfield treated 62 additional patients, some from abroad, who showed significant benefit from being able to access ECMO.

When Glenfield's ECMO unit for children was threatened with closure in 2012, the Director of the ECMO unit at Karolinska, warned that 20 years' experience would be thrown away, and that about 50 babies would die over five years if the unit was moved. "*Leicester has one of the highest survival rates for patients who need ECMO in the world*," he is quoted as saying. Leicester and Karolinska both have survival rates 10 to 20% higher than in other parts of the world (**F**).

Beginnings of evidence-based approach

The novel neonatal trial recruited babies with a predicted mortality of 80%: it also incorporated a prospective health economic evaluation, a follow-up programme and a review of parent opinions of the procedure and the trial. Sir Iain Chalmers of the Cochrane Collection says: "*The trial provided the opportunity to do some important social scientific studies exploring the challenges of explaining controlled trials to parents in the fraught circumstances of the birth of a severely ill child*." (**G**).

It set an important precedent for how research trials should be designed to reduce uncertainty and provide better evidence to inform future decisions in clinical practice and policy implementation. It is one of the earliest examples of direct engagement between NHS Commissioners and academics to assess a new technology prior to any 'creep' into general practice. Chalmers says: "*The example set by British neonatologists when they decided that ECMO should only be offered within the context of a multicentre trial until its effects were clearer remains today a beacon showing the way that clinicians should behave when there is uncertainty about the effects of their practices."* (**G**).

5. Sources to corroborate the impact

A. Specialised Services. Service specification and standard document - Respiratory extracorporeal membrane oxygenation (ECMO) for children and neonates (2012/13) http://www.specialisedservices.nhs.uk/document/10348
B. Daily Mail: Seriously ill newborn baby given tiny ear defenders so he can be flown by helicopter to be closer to his family. 20 July 2013. http://www.dailymail.co.uk/news/article-2371316
C. NHS Specialised Services. Service specification and standard document - Respiratory extracorporeal NHS membrane oxygenation (ECMO) for adults (2012/13) http://www.specialisedservices.nhs.uk/document/service-specification-standards-respiratory-extracorporeal-membrane-oxygenation-ecmo-adults
D. Mugford, M, Elbourne, D., Field D. Cochrane review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants.16 Jul 2008.
E. Petrou, S., Bischof, M., Bennett, C., Elbourne, D., Field, D., McNally, H.. Cost-Effectiveness of Neonatal Extracorporeal Membrane Oxygenation Based on 7-Year Results From the United Kingdom Collaborative ECMO Trial. Pediatrics 2006; 117:1640-1649
F. BBC News: Expert's warning over Glenfield's loss of ECMO. 10 July 2012 http://www.bbc.co.uk/news/uk-england-leicestershire-18783972
G. Statement from founder of the Cochrane Collection and an advocate of non-commercialised controlled trials.