Symposium on ethics and clinical trials

Neonatal extracorporeal membrane oxygenation (ECMO): clinical trials and the ethics of evidence

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Authors’ abstract

Neonatal extracorporeal membrane oxygenation (ECMO), a technology for the treatment of respiratory failure in newborns, is used as a case study to examine statistical and ethical aspects of clinical trials and to illustrate a proposed ‘ethics of evidence’, an approach to medical uncertainty within the context of contemporary biomedical ethics. Discussion includes the twofold aim of the ethics of evidence: to clarify the role of uncertainty and scientific evidence in medical decision-making, and to call attention to the need to confront the irreducible nature of uncertainty.

Neonatal extracorporeal membrane oxygenation (ECMO) is a life-support technique for newborns with respiratory failure who have not responded to conventional ventilation therapy. It involves cardiopulmonary bypass with a modified heart-lung machine to provide gas exchange and thus time for recovery of the impaired lungs. The technology has diffused rapidly in recent years, but its assessment has been the subject of continued controversy (1).

This article uses ECMO as a case study to examine statistical and ethical aspects of clinical trials, including some questions concerning the adoption of medical innovations. The issues are discussed in terms of an ‘ethics of evidence’, proposed by one of the authors as an approach to medical uncertainty to be incorporated into the evolving scope of biomedical ethics (2). The ethics of evidence, meaning – in concise but not exhaustive terms – standards for the creation, assessment, and communication of evidence, calls for interdisciplinary study and further clarification of the concepts of uncertainty and statistical evidence, in a manner that is meaningful to non-specialists.

The first part of the article focuses on statistical and related ethical issues in the ECMO controversy. These are then used to illustrate some aspects of the proposed ethics of evidence. The article concludes with a more general discussion of the problem of coming to terms with medical uncertainty.

A brief history of ECMO

Success in the treatment of neonatal respiratory failure with ECMO was first achieved by Robert Bartlett and his team in 1975 (3). Initial indications for the use of ECMO included severe respiratory failure with a predicted mortality of at least 80 per cent with conventional medical treatment. The early reports were followed in rapid succession by others, from an increasing number of hospitals offering the procedure. As of mid-1992, there were 6,393 registered cases from 84 ECMO centres, 72 in the US and 12 abroad (4). A review of 3,528 cases treated between 1980 and 1989 reported an overall survival rate of 83 per cent; the medical complication rate was 63 per cent (5).

To date there have been two randomized clinical trials (RCTs) for the assessment of neonatal ECMO. The first one, undertaken by Bartlett and his group, was completed in 1984 (6). Since extremely promising results had been obtained with ECMO treatment of neonates and the patients to be entered had an expected mortality of at least 80 per cent, the decision was made to use a so-called randomized play-the-winner scheme (7) in order to minimize the number of patients assigned to the inferior therapy. In this method the assignment of a patient to one or the other treatment is influenced by the clinical outcome for all previous patients in the trial, with increasing probability of assignment to what is being observed as the better treatment. Infants in the control arm were to receive conventional ventilator therapy and informed consent was to be obtained only for infants assigned to ECMO. As it turned out, the study concluded with 12 patients; the one patient assigned to conventional therapy died and all 11 ECMO patients survived. The results, however, met with strong controversy.

The second RCT of neonatal ECMO was carried out between 1986 and 1989 (8) by a team that included investigators who had been critical of the first trial. But this study also utilized an adaptive design, where the course of the trial is affected by

Key words

Perinatal medicine; clinical trials; statistical inference; ethics; uncertainty; evidence.
the observed outcome on previous patients, and informed consent was again obtained only for ECMO patients. In the randomized phase of the trial 4 of 10 infants in the control group on mechanical ventilator support died, and all 9 infants given ECMO survived. In the second phase of the study all patients received ECMO and 19 of 20 survived. The controversy over the trial erupted in the mass media four months before the results were reported in a peer-reviewed medical journal (9).

Beyond the issues of informed consent and other aspects of study design, there has been the question of expected survival with conventional medical treatment. Earlier modes of treatment of respiratory failure generally involved hyperventilation, which was also used for the control groups in the two RCTs. But excellent results were reported for some conditions without ECMO and hyperventilation by Wung and colleagues (10). In a retrospective analysis of hospital records, Dworetz and associates found a sharp rise in survival rates over time of ECMO-eligible patients treated with mechanical ventilation (11), reaching 90 per cent in recent years.

There is a great deal of uncertainty surrounding neonatal ECMO. The pathophysiology of respiratory failure in the newborn is not fully understood. Some of the conditions may be in large measure be iatrogenic; with proper treatment during labour and delivery, the need for ECMO itself could be prevented in many cases. There is a need to determine the diagnostic categories for which ECMO is the necessary and most appropriate treatment. But assessment of effectiveness for well-defined categories of patients is difficult because methods of ventilatory support are changing rapidly, as is ECMO technology itself. As conventional treatment continues to evolve, there is a clear need for concurrent controls for ECMO with the most effective alternative therapy.

At the same time, information on long-term outcome is needed; the late effects of ECMO procedures are uncertain. Several recent reports have linked ECMO to specific brain pathologies. It will be difficult to assess these, and the sequence of evolving ECMO technology, in the absence of cohorts of concurrent controls treated without ECMO.

The spread of ECMO is not entirely in the hands of the physicians. For example, the May 1990 issue of America West Airlines Magazine contained an ad by the Board of City Development of a Southwest city, with the headline: ‘Our ability to save struggling newborns with an ECMO Unit makes [our city] one of the healthiest medical communities in the nation’ (12). Use of ECMO as a marketing tool in a highly competitive health-care system makes its proper diffusion a much more complex problem.

Issues in statistics and ethics
Both RCTs of neonatal ECMO were planned with the collaboration of professional statisticians. Statisticians have also figured prominently in the ensuing controversy, which has included reports in the mass media. The statistical community is sharply divided on the basic issues, even over the need for randomized trials of ECMO. An article on ECMO by James Ware, a critic of the first RCT and collaborating statistician on the second, was published in a statistics journal, followed by a wide spectrum of opinion expressed by 11 other statisticians (13). There are diverse philosophical approaches to the foundations of statistical inference, and these are reflected in the conflicting views on the appropriate way to conduct clinical trials. The range of disagreement about both theory and methodology attests to the health and vigour of the field of statistics, with biomedical application being one of its most active research areas.

Adaptive designs for clinical studies are not new to biostatistics. The development of methodology for sequential medical trials, where termination of the study is determined by the outcome observed for patients already entered into the trial, dates back to the early 1950s; it was motivated to a large extent by ethical considerations, researchers wanting to conclude the trial at the earliest time possible, so that the minimum number of patients would be assigned to the inferior treatment. Data-dependent treatment allocation was proposed in the late 1960s. Although the subject of continued research and lively discussion among statisticians, adaptive designs have never become part of mainstream clinical research methodology.

One potential problem with such designs is the often inadequate sample size for estimating treatment effect once the trial has been terminated. For example, in the first neonatal ECMO RCT the observed 100 per cent mortality for the control treatment was based on a sample size of 1. In the second RCT the randomized phase included only 9 ECMO and 10 control patients.

Another serious hindrance to the acceptance of these designs is the difficulty of conveying their rationale and interpretation to the medical community, especially to clinicians who have personal misgivings about the new treatment. Familiar only with the classical fixed-sample-size design, many feel that these are not really randomized control trials. The adaptive strategies of the two neonatal ECMO RCTs had never been used before, and it does not help that even statisticians disagree as to the validity of the conclusions. Dealing with the complexities of probability theory and statistical inference is a difficult issue in any case, as was documented for example in the study by Berwick and associates concerning physicians’ ability to make inferences from quantitative clinical information (14). This problem extends also to other professional groups concerned with clinical trials, such as philosophers. As increasing numbers of moral philosophers address themselves to ethical aspects
of RCTs, there is a danger that their work may be sidetracked by lack of insight into basic statistical procedures (15).

In addition to the questions of whether there should even have been an RCT, what the proper design should have been, and at what point the trial should have been terminated, there is the ethics of informed consent. In both trials only the families of infants assigned to receive ECMO were told about the study and asked to give informed consent. This procedure, the randomized consent design proposed by Zelen (16), has been controversial in itself and its application in the ECMO trials has been criticized by many. But in any case, even the basic condition of the Zelen design and of randomization in general, that of a state of genuine uncertainty about the two treatments, was in question here. (This condition is expressed by the classical null hypothesis of statistical inference, which states that the two treatments are equally effective in terms of a given outcome measure.) Both teams believed ECMO to be more effective, and this was reflected in the designs of the two studies. For this reason, the concept of ‘clinical equipoise’ suggested by Freedman (17), meaning a state of genuine uncertainty within the expert medical community, does not resolve the problem in this context.

The issues raised by ECMO concerning statistical methodology and the ethics of clinical trials are of a generic nature; they pertain to the assessment of all medical innovations. Similarly, the challenge faced by ECMO with regard to its future development is shared by all of clinical medicine.

Another view of ECMO

A related article, using ECMO as an illustration of ethical issues in medicine, has been published by Lantos and Frader (18). Commenting on it will give us an opportunity to further analyse the situation.

The authors’ assessment of the uncertainty surrounding ECMO is similar to ours, and we share their view that there must be greater acknowledgement of inevitable medical uncertainty. But the attitude they advocate appears to us counterproductive. We do not doubt that, as they note, ‘investigators have been open and honest in their evaluation of ECMO’ and that they did what they thought was best, given the complexity of the situation. This, however, does not mean that the procedures followed cannot and should not be improved. The authors are of the opinion that the development of ECMO ‘illustrates the weaknesses of an approach to clinical research in which randomized, controlled trials are seen as the only gold standard and the ultimate basis for the resolution of medical disagreements’. But it is not necessary to take this extreme position concerning the role of RCTs in order to feel that far more could be done in medical technology assessment than is currently the case.

Lantos and Frader cite six features of ECMO that have made its evaluation troublesome by means of RCTs. Briefly, the problems they cite are: 1) treatment of several different disorders by ECMO; 2) the need to estimate prognosis from historical data in a rapidly evolving field; 3) combination of ECMO with other therapies may be the optimal treatment; 4) both ECMO and conventional therapy are changing rapidly, making completion of clinical trials difficult and current studies of long-term outcome possibly irrelevant; 5) success may depend on practitioner skill as much as intrinsic efficacy; and 6) there are multiple outcome measures.

It is not our intention to minimize these difficulties. It is important to note, however, that they are not unique to ECMO and that they are being addressed with varying degrees of success by others. Questions of study design have also been controversial, and often highly publicized, for major life-threatening diseases such as AIDS and cancer.

Stratification of patients by disease category is a way to approach the first problem, that of diverse disorders being treated with ECMO. Histology and stage are, for example, standard subgroups in cancer trials. Sample size is certainly an issue, but over 6,000 infants have by now received ECMO. Both RCTs allowed for entry of patients with different diagnoses and there was no stratification. In a multicentre RCT of ECMO, stratification by hospital would also have been a standard component of the design, yielding information on variation due to institutional differences such as skill of the ECMO team. Technical skill is a crucial factor in all surgical interventions – coronary artery bypass surgery, for example, which has been studied in large-scale cooperative trials. With well-defined patient categories and protocols, adequate sample size, and complete records on important variables, multivariate statistical analyses can provide useful insights on individual variable effects and interactions.

Rapidly evolving therapies like neonatal ECMO and alternative treatments of respiratory failure must be addressed in series of sharply focused trials. Cooperating groups of investigators must agree on specific protocols and ensure patient accrual at a rate that will permit a succession of studies keeping pace with theoretical and technical developments. Trials of this type have been carried out for other paediatric conditions, such as childhood leukaemia (19). Combination therapy has been studied extensively in cancer. Follow-up studies will achieve greatest relevance if a comprehensive data-base is maintained for concurrent treatment groups of patients. Multiple outcome measures, such as survival, quality of life, and long-term sequelae, are of interest and being considered in the formal assessment of many therapeutic procedures. Clearly, the trial has to focus on an agreed-upon short-term outcome, with careful monitoring of others. Having adequate control groups to follow is essential.
Lantos and Frader state that greater certainty about ECMO could only be attained by sacrificing other important values. They list three: 1) access for patients to potentially efficacious new treatment; 2) participation by patients in choosing their own treatment; and 3) the right of physicians to offer what they believe to be the best available treatment. The first and third of these have been held in high esteem since long before the age of scientific medicine. But the history of medicine provides many examples of promising treatments that proved to be ineffective or even harmful. As for the second value, patient choice of treatment: this has been precisely one of the sources of controversy in the two ECMO RCTs. Patients were not given a choice; the parents of newborns assigned to the control groups were not even informed that there was another treatment.

Proposal for an ethics of evidence

Relevant to these deliberations is the proposal made by one of us for the development of an ‘ethics of evidence’, to focus on the role of evidence in the context of the ethics of modern medicine (2). Reflected here is the belief that better scientific evidence is needed as the basis for meaningful, ethically defensible action in many areas of health care, in both medical practice and public policy. The ethics of evidence is an approach to medical uncertainty concerned with standards for the creation, assessment, and communication of evidence. Its main tenet is twofold, comprising two distinct imperatives: 1) There is a need to develop and disseminate the best possible scientific evidence as a basis for every phase of medical decision-making, and 2) there is a need to increase awareness of, and come to terms with, the ultimately irreducible nature of uncertainty. This dual tenet can be viewed as a newly formulated principle of biomedical ethics. As will be discussed below, the first imperative is supported by the three basic principles of contemporary bioethics, the principles of autonomy, beneficence, and justice. The second imperative extends beyond these.

The principle of autonomy, or respect for persons, gives patients (or their surrogates) the right to make their own decisions about treatment. But the patients cannot give truly ‘informed’ consent if the procedures being recommended have not been properly evaluated. The necessary information is simply not available, and patients and their families are usually not even aware of the extent of medical uncertainty. In the case of ECMO, parents of infants assigned to the control groups in the two RCTs were not told about the trial and thus had no choice concerning the procedure. We believe that strict adherence to the principle of respect for persons would preclude use of the randomized-consent design, concealing from patients the fact that they are part of an RCT. They have a right to know. As for all the patients treated with ECMO before and outside the RCTs, their parents could not give truly informed consent because so many aspects of the technology were and still are poorly understood by the medical profession. Greater attention to medical uncertainty, with better communication between physician and patient, would probably also help alleviate the crisis in malpractice litigation, which is especially serious in perinatal medicine. The extent of future litigation, on behalf of patients who had received or not received ECMO, is as yet unknown.

The principle of beneficence and non-maleficence – help or at least do no harm – has direct bearing on an ethics of evidence. It is unethical to introduce into widespread use powerful diagnostic or therapeutic procedures before they have been carefully assessed for their safety and effectiveness. It follows that clinical studies without proper statistical design, incapable of yielding scientifically valid conclusions, are themselves unethical. By this principle RCTs for ECMO should have been initiated much sooner, with wide-scale co-operation to facilitate carefully designed and monitored multicentre trials. The first RCT began in 1982, seven years after the first successful use of neonatal ECMO. And of the more than 6,000 ECMO patients treated by mid-1992, only 40 – less than one per cent – were evaluated in a randomized trial.

There is a need for greater awareness on the part of physicians of the extent of uncertainty concerning new as well as established procedures. The lack of familiarity of many clinicians with important principles of statistical inference is an underlying problem, resulting in a general tendency to accept claims not supported by scientific evidence. Health care administrators also need to be much more aware of aspects of medical uncertainty and the ethical dimensions of better medical technology assessment.

The question of controversial innovative study designs that fail to convince large segments of even the statistical community remains unresolved. Here again, better communication has to be at least part of the answer. Given the experience with the ECMO trials, perhaps highly unusual new trial designs should be subject to prior review by an interdisciplinary advisory panel knowledgeable about related medical, statistical, and ethical issues.

Finally, greater professional recognition of the kind of time-consuming collaborative effort required for the proper assessment of clinical innovations would provide added incentive for physicians to engage in such activities, called for by the principle of beneficence.

The principle of justice has implications beyond the fair selection of subjects for clinical research. Interpreted to mean equity in access to health care, it supports the ethics of evidence in an indirect way that is especially relevant to the US health-care system. If only medical procedures with established safety and
effectiveness were reimbursed by third-party payers (government plans and private insurance carriers), the savings could provide medical coverage for the millions of Americans now without adequate health insurance. We realize that there is today no general mechanism in the US for converting savings in one area to benefits in another. Our aim is to point out directions for an improved health-care system, as once again health-care reform is high on the political agenda. Our concern here is not with cost containment as an end in itself, but with quality of care. Thus the cost of ECMO taken out of context should not be a determining factor in its use.

The ethics of evidence: a conceptual framework

The intention in suggesting an ethics of evidence has not been to propose another code of medical ethics, but – by formulating a new principle – to promote greater awareness of the pertinent issues. Discussion of the ethics of evidence should be a means of consciousness raising for the health care community as well as the lay public. There is a strong ethical basis for developing the best possible evidence for medical interventions, and this may be the right time for a wider hearing. But the ethics of evidence also entails calling attention to the irreducible nature of uncertainty. Even in a carefully designed study, statistical results are always given in terms of error probabilities, and different methods applied to the same data may yield different conclusions. There is always the problem of patient selection and the type of control used, and there may be other biases that will not be evident until much greater insight has been gained into underlying biological mechanisms of action. All these issues are illustrated by the case of ECMO. The concepts of evidence and uncertainty complement each other in a way well known to specialists in statistical methodology. But there is a great need to study and further clarify these two concepts in an interdisciplinary setting, in terms that are meaningful to other professionals and the public.

The ethics of evidence calls for increased awareness, better communication, and more spirited cooperation. It does not claim to provide a facile resolution of all problems. There will always remain the inherent tension between standards of scientific research and the need to act in a clinical setting. There will be tension in trying to achieve truly informed consent, given the extent of uncertainty about many procedures and the need to foster confidence and a positive attitude in the patient. There will remain tensions between clinical practice and marketing and other economic incentives. For example, if criteria for the maintenance of an ECMO centre include a minimum number of cases to be done per year, say 12 or 24, that in itself will put pressure on clinical staff to bias treatment decisions in favour of ECMO.

Nevertheless, much can be done to influence major factors that affect the diffusion of medical technologies. With good information and proper motivation, decision-making processes can be modified or changed; more effective constraints and incentives can be developed; better evaluation can be achieved; and there can always be improved communication. Rather than urge the ‘pursuit of a chimerical scientific perfection’, the expression used by Lantos and Frader, the ethics of evidence mandates doing the best under the circumstances, in full interdisciplinary co-operation. This means a persistent grappling with uncertainty, using the insights and most up-to-date tools each discipline has to offer.

Acceptance of the ethics of evidence in turn leads to the notion of personal responsibility as a necessary counterpart to the principle of autonomy. Confronting the uncertainties inherent in medical evidence carries special responsibilities for health-care professionals and policy-makers, philosophers and educators, the media, and the general public (20).

In all of this, there is a special challenge facing the statistical profession. Responding to the obvious need, it must continue its own research programme, while strongly urging better assessment of medical technology. But at the same time it must find more effective ways of conveying to others the great complexity and the basically ambiguous nature of statistical methodology. The formal procedures of a mathematical discipline can never be the sole determining factor for judgements about practical action, especially in medicine.

Arnold Relman has characterized American medicine as being on the threshold of the third revolution in health care since World War II (21). After the Era of Expansion, which lasted from the late 1940s through the 1960s, and the subsequent Revolt of the Payers or the Era of Cost Containment, we now see the dawning of the Era of Assessment and Accountability. This means the development of a strong consensus concerning the need for better information on the safety, effectiveness, and relative cost of medical procedures and on the general functioning of our health-care system.

Paul Ellwood has called for a national programme of ‘outcomes management’ or a ‘technology of patient experience’, which would involve a permanent national medical data-base, linking medical interventions with health outcomes (22). In his words, ‘the fine line between chaos and democracy is rationality of choice’, and ‘the health care system has become an organism guided by misguided choices; it is unstable, confused, and desperately in need of a central nervous system that can help it cope with the complexities of modern medicine’.

Ellwood speaks of the need for a central nervous system in American health care, a system for coordination and control. This is indeed a powerful
metaphor, but one that must be handled with caution. A reductionist approach will not do. Whatever the structure, the key functions are performed by human beings. He himself states that his proposed system 'is absolutely dependent on the participation and co-operation of the entire health enterprise'. Relman has also noted that the new Era of Assessment and Accountability will require 'unprecedented co-operation.' This surely entails full awareness of the issues involved, coupled with a strong sense of personal responsibility on the part of both health-care professionals and the public. It seems to us that widely accepted guidelines will be needed to influence behaviour and foster co-operation – to express the new moral imperative engendered by the situation. An ethics of evidence such as discussed here may provide the necessary conceptual framework – a 'mind' to direct the proposed 'central nervous system'.

Considered in its full context, the concept of the ethics of evidence is in no way weakened by current critiques of 'principlism' (23). It can be seen instead as an integral part of whatever meaningful structures may evolve in future biomedical ethics.

Medical uncertainty in broader perspective

Jay Katz sees as a key problem of contemporary medicine the inability of many doctors to acknowledge medical uncertainty in their interaction with patients. Discussing the use of placebos in RCTs, he said: 'It is this encounter with the subject that is the great problem and not the ethics of randomization, of placebo-controlled studies, or of exposure of subjects to risk, or of preferring future over present subjects' (24).

Part of the motivation of physicians for not being open with patients is no doubt the desire to spare them further anxiety. In describing the conditions surrounding the treatment of seriously ill newborns, Karen Lebacqz has compared the suffering endured by the parents of these infants to the wilderness experience of the Israelites in the Old Testament (25). Loss of control and recurring uncertainty were important aspects of this experience. Sensitivity to their suffering was a reason that parents of children who were not to get ECMO in the two RCTs were not told about the trial. But recourse to paternalism is not necessarily the solution to the problem, as may become evident in future ECMO-related litigation.

Implicit in a better understanding of the relationship between evidence and uncertainty, called for by the ethics of evidence, is the need to come to terms with uncertainty. The practice of medicine touches on questions that are far beyond the scope of science – the fundamental questions of life, illness, suffering, and death. The total openness and awareness advocated by the ethics of evidence will keep in constant view the ultimate uncertainty of the human condition. As a consequence, attention may more readily focus on cultural resources that in the past have provided humanity with meaning. Central among these are support of the community and insights offered by our great religious traditions, which have played an important role in the development of modern society. They seem worthy of consideration in the reasoned analysis that is the common language of today's pluralistic system, as we contemplate the future of high-technology medicine.

Conclusion

Much about the introduction and diffusion of ECMO can serve as a lesson for the biomedical community, as can the challenges that remain. The full evaluation of this life-saving technology and its long-term consequences need yet to be completed, and the studies required will likely call for still greater co-operation. The further proliferation of ECMO and its role in the hospital marketing scheme are open to question; but health-care administration also falls within the scope of the proposed ethics of evidence.

One of the most eloquent spokesmen for the careful assessment of medical innovations has been William Silverman, a neonatologist. Silverman has for years been urging not only better and more timely clinical trials, but also an ever vigilant attitude of 'epoché', or suspended judgement (26). Demanding the best possible scientific evaluation at every step along the way, while ceaselessly sharing the extent of our uncertainties, is we believe the only way to promote the full development and best utilization of medicine's enormous potential.

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in an appropriate register of clinical trials as soon as one exists.

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References


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