Informed consent and research design in critical care medicine

Robert D Truog

Address: Associate Professor, Anesthesia and Pediatrics, Harvard Medical School and Multidisciplinary Intensive Care Unit, Children's Hospital, Farley, Boston, MA 02115, USA. Tel: 617 355 7327

Received: 15 June 1999
Accepted: 22 June 1999
Published: 3 July 1999

Crit Care 1999, **3**:R29–R33

 ISSN 1364-8535

The Nuremberg Code recently celebrated its 50th birthday, marking the progress that has been made in ensuring respect for human rights both within and beyond the context of medical research [1]. Today, many journal editors will refuse to consider manuscripts that have not undergone formal review by an independent committee, and virtually none will publish results that were procured without the explicit informed consent of the subjects. In one sense, therefore, the bioethics movement of the past several decades seems to have scored a resounding victory.

In another sense, however, the rapid pace of medical research and the increasing effectiveness of medical interventions have only intensified the ethical dilemmas that physicians encounter in clinical research. The intensive care environment, in particular, has several characteristics that provide especially difficult challenges to the standard requirements of informed consent for research. I will highlight three features of this environment that may call for innovative or alternative approaches to both study design and the process of informed consent to both respect the rights of the research subject and permit the continued accrual of medical knowledge.

First, many trials performed in critical care medicine involve experimental treatments that have the potential to be life saving. Patients who are eligible for studies in the intensive care unit (ICU) are often extremely ill, and standard therapy may have little or nothing to offer. While clinicians may be able to take a dispassionate stance and insist that from the perspective of the medical scientist there is no evidence that the experimental therapy is superior to conventional treatment, the patient or family may have a very different impression. They may hold the firm belief that the experimental treatment offers the only significant hope for the patient's survival. From their perspective, randomization may not represent the process of choosing between two equally effective alternatives, but rather may be a seen as a coin flip between a chance for survival and an almost certain death. Indeed, there is evidence that families misperceive the process of randomization as a mechanism for triaging patients when a therapy is too scarce to offer to everyone [2]. This feature of ICU research creates intense ethical conflicts for clinical researchers, and will be explored in more detail below.

The second characteristic aspect of intensive care research that leads to unique ethical issues is the fact that very few of the potential research subjects are capable of engaging in a discussion of informed consent. Either patients are too heavily sedated to permit their participation in deliberations about their care, or they are acutely ill and decisions about inclusion into trials need to be made on an emergency basis (*eg* trials of alternative modes of performing cardio-pulmonary resuscitation). The former problem has had a relatively straightforward solution in the USA, where both ethics and law have almost uniformly recognized the legitimacy of surrogates to make medical decisions for incompetent patients, including in most cases providing consent for therapeutic research. This is often not the case in Europe, where surrogate decision-making remains more controversial [3].

The difficulties of performing research on emergency interventions was recently recognized in the USA by the Department of Health and Human Services, which responded by creating an emergency exemption to informed consent in situations where the experimental intervention must be introduced emergently and where the patient is both unable to consent and surrogate decision-makers are not available [4]. This exemption has been strongly opposed by some critics as a dangerous precedent away from an uncompromising commitment to informed consent for research, but several trials utilizing this intervention are currently under way [5].

The third characteristic of the critical care environment that places unique demands upon research is the often rapidly changing and developing nature of the technologies being tested. Many ICU interventions involve complex technical procedures or sophisticated mechanical devices [*eg* extracorporeal membrance oxygenation (ECMO), continuous venovenous hemofiltration (CVVH), high-frequency oscillatory ventilation (HFOV)] that have a steep learning curve and that undergo almost continual evolution through the 'tinkering' of skilled and creative clinicians. This creates an inevitable tension in the efforts of researchers when they want to show that these new techniques are an improvement over previous therapies. On the one hand, it is important that the clinicians develop these

ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation; CVVH = continuous venovenous hemofiltration; HFOV = high-frequency oscillatory ventilation.

interventions to the point where they feel they have mastered the most critical technical challenges and have overcome the major hurdles of applying the technology to critically ill patients. On the other hand, it is important that the clinicians not miss a 'window of opportunity' for rigorously comparing these new technologies against standard therapy in a formal clinical trial, before the technologies become uncritically and widely accepted into clinical practice.

This inherent tension is compounded by the need to standardize the treatments in both the experimental and control arms of a clinical trial. Consider, for example, recent clinical trials of neonatal ECMO in the USA and the UK. Each of these trials took several years to complete. During these intervals, ECMO technology underwent continuous evolution, ranging from developments in catheter design to alternatives in anticoagulation to new surgical approaches (such as venovenous ECMO as an alternative to venoarterial, repair rather than ligation of the carotid artery). Similarly, during the time-frame of these trials there were major innovations in nonECMO interventions, such as the emergence of HFOV, nitric oxide therapy, and permissive hypercarbia. During the period of the trials, centers performing under protocol had to accept a virtual freeze on any inclination to either tinker with their approach to ECMO or to introduce any modifications to the 'control' protocols. This moratorium on innovation impacted the trials in two major respects: first, by the end of the trials, the families of children in the control arm could no longer be assured that they were in fact receiving the best standard clinical care (since centers not involved in the protocol had progressed to using alternative strategies); second, evolution in the technology of ECMO itself was sufficiently different by the end of the studies that the results of the trials could truthfully only be said to apply to a form of ECMO that was already obsolete. The moral of the story is this: when both the experimental therapies and the standard therapies are in rapid evolution, standard approaches to comparing them through formal clinical trials are often too time-consuming, leading to restrictions on clinical innovation and results that are already obsolete by the time they are published.

Each of these three considerations raises interesting questions about how to modify our approach to research in the ICU in ways that will continue to respect the fundamental principles of Nuremberg while continuing to allow for the advancement of medical knowledge. In the remainder of my comments, I will return to the first issue cited above, namely the conflicts that occur when experimental therapies are potentially life saving.

Perhaps the most fundamental ethical dilemma in medical research concerns the potential for conflict of interest between the roles of the physician as clinician versus the physician as scientific investigator. Acting in the role of clinician, the physician's highest priority is the welfare of the individual patient. The goals of the scientific investigator, on the other hand, are focused upon the acquisition of medical knowledge in order to benefit future patients. One recent paper characterized this dichotomy in terms of 'individual ethics' versus 'collective ethics', or 'doing what is best for current subjects in the trial versus doing what is best for future patients who stand to benefit from its results' [6].

How does the clinician resolve the conflict between these divergent roles? One suggestion has been to insist that the clinician be in a state of equilibrium, or 'equipoise', regarding the relative efficacy of the various treatments being studied. In other words, if the clinician is completely undecided as to which of the treatments is best, then there is no conflict of interest in choosing between these treatments by the 'flip of a coin'.

This standard, described as 'personal equipoise', has long been recognized as being too stringent. To begin with, virtually all clinical investigators enter into clinical trials with the belief that their intervention is superior to existing treatments. Otherwise, why would they spend the enormous amounts of time and energy involved with performing the studies necessary to demonstrate this superiority? Furthermore, based upon their personal experience and individualized reading of the literature, clinicians frequently have strongly held opinions about which of the alternative interventions is the most effective, even if the published evidence is far from conclusive. Under the personal equipoise standard, these clinicians would be ethically barred from participating in randomized comparisons of these interventions.

Benjamin Freedman is generally credited with proposing an escape from this dilemma, based upon the concept of 'clinical equipoise' [7]. Clinical equipoise exists when there is uncertainty about the relative efficacy of alternative treatments within the medical community as a whole. Freedman claimed that a state of clinical equipoise is necessary for physicians to ethically enroll patients in clinical trials. It is not necessary for a clinician to be in personal equipoise in order to enroll a patient, Freedman argued, so long as there is genuine uncertainty within the medical community, *ie* so long as there is a state of clinical equipoise.

The concept of clinical equipoise has been very useful in relieving the ethical tensions between clinicians and investigators in most types of clinical trials. To give an example, if I believe that a new β-blocker offers advantages over those currently on the market, I can, with a clear conscience, enroll my patients in a randomized trial that compares the new medication with another that is standardly available. I simply explain to my patients that, even though

I have a hunch that the new medication will eventually prove to be better than the alternatives, they should be willing to have their therapy determined by a flip of the coin, since there is as yet no convincing evidence to support my belief in the superiority of the new drug.

The concept of clinical equipoise is less convincing, however, when it is used to justify the randomization of treatments that have the potential to be life saving. I will use the history and development of neonatal ECMO as a paradigmatic type of ICU research that also provides an excellent case study for exploring this issue [8].

ECMO emerged in the 1960s when development of the membrane oxygenator permitted the use of cardiopulmonary bypass for periods of more than a few hours. Although early efforts in the use of ECMO for adults with acute respiratory failure were disappointing, interest persisted in the use of ECMO to treat neonatal respiratory failure. Robert Bartlett therefore used this new therapy to treat 16 critically ill infants, and reported six survivors. Encouraged by these initial results, Bartlett continued to develop the technology, and by 1980 achieved 75% survival in patients judged to have a 95% mortality when managed with conventional therapy [9]. Despite this success, many remained skeptical about the effectiveness of ECMO in the absence of a formal clinical trial. Bartlett realized the need for a rigorous comparison of ECMO against standard therapy, but was concerned about denying some patients a therapy he viewed as potentially life-saving.

Should Bartlett have relied upon Freedman's concept of clinical equipoise, and proceeded with a randomized clinical trial comparing ECMO against standard therapy? In 1980 there was clearly uncertainty within the medical community about the relative benefits of ECMO, and indeed most neonatologists were biased against it. Yet I believe that Bartlett was correct in viewing clinical equipoise as an inadequate justification for proceeding with a traditional randomized comparison of ECMO against standard therapy, for at least two reasons.

First, imagine what doctor–patient relationships would be like if doctors always took clinical equipoise seriously. Imagine a physician saying, 'My personal opinion would be to begin antibiotics for possible sepsis in a patient with your signs and symptoms. Nevertheless, since there is disagreement about this in the medical literature and the medical community more generally, I will decide whether or not to start you on antibiotics by flipping a coin'. Such a doctor would probably command little respect from his patients or colleagues, yet this is precisely what is demanded of the doctor when enrolling patients in clinical trials.

Second, the structure of randomized clinical trials often requires them to continue beyond the point at which clinical equipoise has already dissolved. Consider a hypothetical trial that, based on power calculations, is scheduled to enroll 1000 patients. Suppose that almost all of the patients have been enrolled, and that the P value is already well below 0.05. Based upon standard research procedure, however, the investigators are forbidden from analyzing the data until all of the patients have been enrolled (I am here ignoring the possibility of early stopping rules). Assuming that the outcomes from the few remaining patients do not have the potential to raise the P value above the significance threshold, then all remaining patients who are randomized into the control arm of the study will receive a treatment that will soon be shown to be inferior to the alternative.

What ethical justifications could be offered to defend the randomization of these remaining patients into the control arm of the study, other than a justification (based upon a 'collective' rather than an 'individual' ethic) that sacrifices the best interests of these patients in favor of producing knowledge that will benefit future patients? While some patients may find this sacrifice acceptable for many types of trials (*eg* the β-blocker study mentioned above), few would be willing to risk their lives by not receiving the superior treatment, especially if the value of their sacrifice was only to move the P value a little lower below the level of 0.05.

Perhaps it was these types of concerns that led Bartlett to decide not to proceed with a traditional randomized clinical trial in the evaluation of neonatal ECMO. The approach that he adopted is one that has emerged within a growing literature by statisticians who are sensitive to the ethical concerns that may arise in randomized trials such as these [6,10–14]. They have developed a number of innovative and intriguing alternatives to traditional randomized trials that seek to mitigate the inherent tension between the goals of the physician as clinician and the goals of the physician as scientific investigator. I believe these alternatives have been underutilized in the design of clinical trials in critical care medicine, and that the interests of individual patients have been unduly sacrificed to the interests of medical knowledge and future patients. As one recent statistical review of these alternative approaches concluded, 'when circumstances are appropriate, the failure to exploit modern statistical methodology and information technology is indefensible in present day clinical trials' [6].

Bartlett chose one of the more straightforward (and intuitively compelling) alternative statistical techniques known as 'adaptive randomization'. Simply put, adaptive randomization strategies alter the randomization scheme so that more patients are assigned to the treatment that is proving to be more successful. These methods are often described as 'play the winner' strategies, although it would be more accurate to refer to them as 'play the leader'.

Bartlett's randomization strategy began with 'balanced' or 50/50 randomization of the first patient to either conventional treatment or ECMO, with the randomization of subsequent patients heavily weighted toward whatever therapy was proving more successful. Unfortunately, by heavily biasing the randomization in this way, he ended up with a very skewed distribution between the two treatments. Eleven patients were assigned to ECMO, and all survived. Only one patient was assigned to conventional therapy, and this child died [15].

This study illustrates that, when adaptive randomization is taken to an extreme, it may produce results that, while perhaps statistically sound, are clinically unconvincing. The Bartlett trial was therefore widely criticized, and in an editorial that accompanied the published manuscript, a statistician and neonatologist from Harvard claimed that a better study was needed before the superiority of ECMO could be accepted [16].

Not surprisingly, however, when this same Harvard team met to design a better trial, they faced the same ethical dilemma that had plagued Bartlett. In addition to Bartlett's published experience, a national ECMO registry was also accumulating data that showed impressive survival rates with ECMO. A 1988 review of 715 newborns treated with ECMO, for example, demonstrated 81% survival with ECMO and indicated that ECMO was statistically superior to any other treatment with a survival rate less than 78.4% [17]. Few neonatologists at that time could have argued that survival rates of critically ill newborns managed without ECMO were anywhere close to 78.4%.

As a result, the Harvard team also decided to use an adaptive randomization design, choosing only to be less extreme than Bartlett. In the Harvard design, patients were randomized 50/50 to either ECMO or conventional treatment until there was a fourth death in either arm of the study (Phase 1); at that point, all future patients were randomized to the more successful arm, and this was continued until statistical significance was achieved (Phase 2) [18].

Using this more conservative design, the Harvard study achieved more convincing results. During Phase I, nine patients were assigned to ECMO and all survived. Ten patients received conventional therapy; six survived and four died. With the fourth death in the conventional arm, Phase II began. An additional 20 patients were enrolled to receive ECMO; 19 survived and one died. At this point ECMO was judged to be statistically superior to conventional therapy. In retrospect, four patients died who might have survived if they had been offered ECMO. Nevertheless, this was a smaller number than would have died if the trial had been designed with traditional 50/50 randomization. To this extent, adaptive randomization was successful in both demonstrating the superiority of ECMO and in reducing the total number of deaths.

Given the ethical advantages of adaptive randomization designs, why are they not used more frequently in the evaluation of potentially life saving therapies in intensive care medicine? 'Adaptive methods should be used as a matter of course', remarked statistician Weinstein in *The New England Journal* [19]. 'It never pays to commit oneself to a protocol under which information available before the study or obtained during its course is ignored in the treatment of a patient' [19].

Despite endorsements like this, adaptive randomization, as well as other statistically sound alternatives to the traditional randomized trial, continue to be utilized rarely. Some have suggested that this bias is based upon a reluctance to take a risk in the highly competitive process of grant proposals, but many factors are probably involved [6].

The ECMO story itself provides a striking example of this prejudice against adaptive randomization designs. In the early 1990s, the UK was considering whether to adopt ECMO into its armamentarium of treatment for neonatal respiratory failure. After considering all of the above evidence, clinicians in the UK concluded that the superiority of ECMO to conventional management was still in doubt, and that a traditional randomized controlled trial was needed before accepting ECMO for widespread use in the UK. Between 1993 and 1995, 185 newborns were randomized into a traditional trial of ECMO versus standard therapy. The trial was stopped early on the advice of a data monitoring committee when preliminary evidence showed a clear advantage of ECMO. Overall, 30 of 93 infants allocated to ECMO died, compared with 54 of 92 allocated to conventional care ($P = 0.0005$) [20].

Certainly there are no grounds to impugn either the motives or the intentions of the researchers from the UK who conceived and executed this trial. Nevertheless, just as some have questioned whether clinical equipoise existed at the time of the Harvard ECMO trial, I think it is fair to ask whether clinical equipoise existed at the time of the UK ECMO trial, and whether the trial thereby met one of the standard ethical requirements for clinical research [21]. In any case, the UK trial served to illustrate the bias that currently exists against accepting the results of trials that employ adaptive randomization, and, by extension, any other alternatives to the traditional approach.

The UK trial also raises questions about how we determine which treatments should be considered 'experimental' and which 'control'. Given the evidence gathered from clinical experience and research in the USA prior to 1993, a good case could have been made for at least presuming

the superiority of ECMO over conventional management. If so, then perhaps patients who were eligible for the UK trial but whose families refused to participate should have been offered ECMO as the 'control' treatment, rather than so-called conventional therapy [21].

The development of ECMO has perhaps provided as many interesting questions and insights into the process of study design and informed consent as it has into the management of neonatal respiratory failure. The UK investigators have continued this tradition by expanding upon their trial to explore the experiences of the families who were involved to learn more about their attitudes toward informed consent and alternative schemes of randomization [2,22,23]. ECMO has therefore been a paradigmatic case study for many of the types of trials that have been and will be performed in intensive care medicine. We should not lose the opportunity to learn from these experiences, since, as Santayana observed, 'those who cannot remember the past are condemned to repeat it'.

References

1. Shuster E: **Fifty years later: the significance of the Nuremberg Code.** *N Engl J Med* 1997, **337**:1436–1440.
2. Snowdon C, Elbourne D, Garcia J: **Zelen randomization: attitudes of parents participating in a neonatal clinical trial.** *Controlled Clin Trials* 1999, **20**:149–171.
3. de Wachter MA: **The European convention on bioethics.** *Hastings Cent Rep* 1997, **27**:13–23.
4. Anonymous: **Final Rule.** *Federal Register* 1996, **61**:51498–51533.
5. Pearson KS: **Emergency informed consent.** *Anesthesiology* 1998, **89**:1047–1049.
6. Palmer CR, Rosenberger WF: **Ethics and practice: alternative designs for phase III randomized clinical trials.** *Controlled Clin Trials* 1999, **20**:172–186.
7. Freedman B: **Equipoise and the ethics of clinical research.** *N Engl J Med* 1987, **317**:141–145.
8. Truog RD: **Randomized controlled trials: lessons from ECMO.** *Clin Res* 1993, **40**:519–527.
9. Bartlett RH: **Extracorporeal oxygenation in neonates.** *Hospital Practice* 1984, **April**:139–151.
10. Altman DG, Whitehead J, Parmar MKB, Stenning SP, Fayers PM, Machin D: **Randomised consent designs in cancer clinical trials.** *Eur J Cancer* 1995, **31A**:1934–1944.
11. Palmer CR: **Ethics and statistical methodology in clinical trials.** *J Med Ethics* 1993, **19**:219–222.
12. Rosenberger WF, Lachin,JM. **The use of response-adaptive designs in clinical trials.** *Controlled Clin Trials* 1993, **14**:471–484.
13. Royall R: **Ethics and statistics in randomized clinical trials.** *Stat Sci* 1991, **6**:52–62.
14. Trochim WM, Cappelleri JC: **Cutoff assignment strategies for enhancing randomized clinical trials.** *Controlled Clin Trials* 1992, **13**:190–212.
15. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW: **Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study.** *Pediatrics* 1985, **76**:479–487.
16. Ware JH, Epstein MF: **Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study.** *Pediatrics* 1985, **76**:849–851.
17. Toomasian JM, Snedecor SM, Cornell RG, Cilley RE, Bartlett RH: **National experience with extracorporeal membrane oxygenation for newborn respiratory failure. Data from 715 cases.** *ASAIO Trans* 1988, **34**:140–147.
18. ORourke PP, Crone RK, Vacanti JP, Ware JH, Lillehei CW: **Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study.** *Pediatrics* 1989, **84**: 957–963.
19. Weinstein MC: **Allocation of subjects in medical experiments.** *N Engl J Med* 1974, **291**:1278–1285.
20. Field D, Davis C, Elbourne D, Grant A, Johnson A, Macrae D: **UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation.** *Lancet* 1996, **348**:75–82.
21. Lantos JD: **Was the UK Collaborative ECMO Trial ethical?** *Paediatr Perinatal Epidemiol* 1997, **11**:264–268.
22. Snowdon C, Garcia J, Elbourne D: **Making sense of randomization; responses of parents of critically ill babies to random allocation of treatment in a clinical trial.** *Soc Sci Med* 1997, **45**:1337–1355.
23. Snowdon C, Garcia J, Elbourne D: **Reactions of participants to the results of a randomised controlled trial: exploratory study.** *BMJ* 1998, **317**:21–26.