science because most treatment advances are of a modest evolutionary nature that would be very difficult to detect with even well-run observational studies (Dupont, 1985).

It should also be noted that the contemporary survival rates of patients who did not receive ECMO were not nearly as grim as Bratlett et al. (1985) suggest. For example, O'Rourke et al. (1989) observed a survival rate of 60% for patients on conventional therapy in the early 1980s while Dworetz, Moya, Sabo, Gladstone and Gross (1989) reported a survival rate of 90% in patients who received conventional therapy in 1986. Indeed it is far from clear that Bartlett's group could not have conducted an ethical RCT of conventional design if they had been able to provide the best available non-ECMO therapy as the alternate treatment. (See Lantos and Frader, 1990, for a concise review of this literature.)

In spite of the preceding reservations, the issues raised by Royall cannot be easily dismissed. Patients with serious illness are highly vulnerable, and the task of obtaining truly informed consent from them can be exceedingly difficult. This is particularly true when the patient has the option of receiving either of the treatments under study outside of the trial. Currently we are using an egregious double standard in which new pharmacologic treatments must be rigorously evaluated before they become generally available, while new surgical procedures are immediately offered to anyone with the ability to pay. I believe that society has a right to expect that generally available treatments have known and acceptable levels of efficacy, and that new treatments will be evaluated in a way that will lead to continued progress in medicine. The ethical problems of randomizing a patient to an experimental or standard therapy are greatly simplified if the patient's only chance of obtaining the experimental therapy is by entering the experiment. A truly informed consensus as to the ways in which human experimentation should be performed can only be obtained through public debate and the political process. Perhaps the most reasonable position to take is that the *personal care principle* should be followed except in those situations where a political consensus, codified in law, has been reached to the contrary. Our current laws on experimental medical treatments arose, in part, as a backlash to the snake oil salesmen of the 19th century who victimized countless sick and vulnerable patients with worthless or harmful elixirs. These laws mandate the conduct of RCTs prior to making new drugs available to the general public. I believe that most of the ethical issues raised by Royall could be resolved by applying similar regulations to all medical and surgical treatments. With suitable safeguards to protect human subjects, randomized clinical trials can provide an ethical and the optimal means of advancing medical science in societies that wish to protect patients from the adverse effects of unproven therapies while searching for improved treatments for patients in the future.

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Comment

Robert J. Levine

I agree completely with Richard Royall's conclusion that in some situations in which clinical investigations are "badly needed... nonrandomized controls are the only ones that can be obtained ethically" (Levine, 1986, pages 185–212). Here I shall comment on two components of the analysis which led him to this conclusion: (1) The values of science are portrayed as distinct from and generally, at least potentially, in opposition to those of ethics. (2) The physician's competent judgment is viewed as the dominant factor in determining his or her responsibility with regard to recommending therapies to the patient.

1. I am aware of no substantive challenge to the widely held conviction that the randomized clinical trial is the most scientifically sound approach to

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determining which of two medical therapies is superior. Indeed, the randomized clinical trial is often referred to as the "gold standard" in this field. This prevailing perception of the value and validity of the randomized clinical trial notwithstanding, there have been in recent years serious challenges to the ways in which randomized clinical trials are typically designed, executed and analyzed. All too often, and in my view unfortunately, these challenges take the form of pitting the values of science against those of ethics. As Royall puts it, "many randomized clinical trials are beset by reservations and discomforts arising from ethical considerations." Challenges of this type do not acknowledge that the considerations that established the randomized clinical trial as the gold standard in the first place are fundamentally ethical considerations. Such challenges create the appearance of an adversarial relationship between scientists and ethicists—"us versus them"—and make it unnecessarily difficult for thoughtful commentators such as Royall to accomplish their salutary objectives.

The ethical nature of biomedical research may be brought into focus by considering its purpose. The central purpose of research in the field of therapeutic innovation is to develop therapies that will accomplish the goals of curing or preventing diseases or of ameliorating their manifestations. This purpose is both grounded in and responsive to the basic ethical principle of beneficence which, as interpreted by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research embodies two general rules: "Do no harm," and, "Maximize possible benefits and minimize possible harms" (National Commission, 1978a).

In the context of medical practice, considerations of beneficence are expressed in such familiar maxims as *primum non nocere* (first do no harm) and Hippocratic Oath's "I will use treatment to help the sick according to my ability and judgment." In biomedical research, the leading ethical codes such as the Declaration of Helsinki enjoin the physician-investigator not only to secure the well-being of individual patients and subjects (individual beneficence) but also to develop information that will form the basis of being better able to do so in the future (social beneficence). (The Declaration of Helsinki and the Nuremberg Code are reprinted in Levine, 1986.)

There is not only an ethical obligation to develop information that will enhance the capacities of physicians and other health professionals to serve patients' well-being. (For a discussion of the nature and limits of this obligation; see Levine, 1990.) Considerations related to the purpose of research place ethical limits on the justification of research. According to the Nuremberg code, for example, the risks of research must be justified by "the humanitarian importance of the problem to be solved by the experiment." Moreover, there is a general consensus that research cannot be justified ethically unless it is designed sufficiently well that there is a reasonable expectation that it will accomplish its purpose. The National Commission (1978b, page 22) articulated this consensus in a negative form: "Subjects should not be exposed to risk in research that is so inadequately designed that its stated purposes cannot be achieved."

These are the principal considerations that underlie the ethical justification of the randomized clinical trial. Its ethical justification lies in the fact that it is the most effective and efficient means available to pursue the central purpose of biomedical research in the field of therapeutic innovation. It is grounded in the duty to maximize social benefit by developing information that will enhance physicians' future capacity to secure the well-being of patients.

The aforementioned challenges to the randomized clinical trial do not reflect opposition between the values of research and those of ethics. Rather, most of them reflect concerns that, in the design and conduct of randomized clinical trials, there may be too narrow a focus on the value of social benefits, that such design and conduct should be more responsive to other often competing ethical values such as beneficence for individual patients (the patient-centered ethic of medical practice), respect for the autonomy of patients and research subjects (typically expressed in the form of a requirement for informed consent), and justice (or fairness) in the distribution of the burdens and benefits of research (Levine, 1986).

A high level of confidence in the validity (absence of error) of the results of a randomized clinical trial is typically the dominant concern in its design. As Sackett has observed, "validity has become a non-negotiable demand; hence the ascendancy of the randomized clinical trial" (Sackett, 1980). Validity is a value arising from considerations of social rather than individual beneficence. In the design of clinical trials other values must taken into account. Two other values grounded in social beneficence are often in competition with validity as well as with each other: generalizability (the results are widely applicable) and efficiency (the trial is affordable and resources are left over for patient care and other health research).

In the interests of efficiency, clinical trialists

often select as subjects patients who are at high risk of developing the outcome measures or endpoints promptly. Such practices often compromise generalizability. For example, the Lipid Research Clinics Program (1979) trials studied the effects of lowering cholesterol levels on the rate of heart attacks in men who had already had a heart attack. Consequently, this trial cost less money and took less time than it would have had it included subjects at lesser risk. By the nature of its design, therefore, it left open the question of whether men who had not had previous heart attacks or women could profit from lowering cholesterol levels. Also in the interests of efficiency, clinical trialists may reduce the number of subjects to be studied in a randomized clinical trial. This has obvious implications for validity in that it increases the likelihood of errors.

Implicit in the prevailing practice of trading off randomized clinical trial design features in the interests of validity, generalizability, and efficiency is a concept that has been called "sufficient validity for our purposes." (For a more complete discussion of this and related concepts, see Levine, Levine and Dubler, 1991.) This concept permits such statements as this: "While we would have more confidence in the result if the p value were less than 0.01, we shall settle for a p value of less than 0.05 because it is not worth the additional $500,000 the additional confidence would cost." Similarly, one may refer to "sufficient generalizability for our purposes." Hence, although men who had not had heart attacks and women were excluded from the Lipid Research Clinics Program trial, doctors recommend that they lower their cholesterol levels, reasoning that these patients are sufficiently like the study subjects to justify the recommendation.

Just as it is essential to balance the demands of validity, generalizability and efficiency against each other in the design of clinical trials, it is equally essential to balance each of these against considerations grounded in individual beneficence, patient's autonomy and equitable distribution of both burdens and benefits. Just as it is unethical to place subjects at risk in a study whose design is so flawed it cannot yield valid (sufficiently valid) data, it is unethical to ignore individual subject's welfare and rights to conduct a flawlessly designed study. For example, although it would enhance the efficiency of randomized clinical trials to dispense with the informed consent requirement, it is generally agreed that such an action would be an unacceptable violation of patients' rights to self-determination. It is not that the values of science are pitted against those of ethics. It is rather that the value of efficiency in this case is not seen in our society as having a higher priority that that of self-determination. In some other cases, efficiency has been seen as holding a higher priority than self-determination—e.g., mandatory vaccinations.

Scientists and clinicians are accustomed to accepting data obtained by many types of research designs in order to establish efficacy of various types of therapies. There differences are not simply matters of taste or preference. Rather, they reflect a balancing of the requirements of various relevant values. For example, since patients would not knowingly accept sham surgery, studies of surgical techniques may use historical controls, "no treatment" controls or comparisons with patients who either elect or who are randomly assigned to medical management rather than surgery. Evaluations of psychotherapy may use "waiting list" controls (Richman et al., 1980). Although the use of nonrandomized designs is often associated with some loss of confidence in the reliability of the results of a clinical trial, when used appropriately nonrandomized designs can provide sufficient confidence for the purposes at hand. There is, for example, sufficient confidence that penicillin is effective for treating pneumococcal pneumonia, that appendectomy is effective for appendicitis and that digitalis is effective for congestive heart failure to conclude that randomized clinical trials are not necessary and could not be justified.

2. Royall argues that the clinician is "bound by the personal care principle to make a therapeutic decision solely on the basis of what, in his professional judgment, is best for this individual patient...." Since he insists that this must be a competent judgment—a judgment made by a competent clinician—I agree. But what is a competent judgment?

I agree with Royall that a competent judgment need not necessarily conform with some broad professional consensus. The consensus may be wrong. On the other hand, physicians are required to conduct their practices and make their therapeutic recommendations according to "the community standard," a standard used in malpractice litigation to evaluate claims of negligence on the part of physicians. Those who would depart from the community standard bear a heavy burden of proof to justify such departures.

Some clinicians have formed judgments as to what is the "best available therapy" in response to meager data derived from pilot studies. Based upon such judgments they have helped patients falsify eligibility criteria for randomized clinical trials so that they could get a 50% chance at receiving the

"best available therapy" (Melton et al., 1988). Some have advised patients to enroll in randomized clinical trials with the covert intention of withdrawing if randomized to the "inferior arm" (Marquis and Stephens, 1989). These are not ethically acceptable behaviors and they do not necessarily reflect competent judgments (Levine, 1989).

Suppose there is a randomized clinical trial comparing therapy A with therapy B in the treatment of condition C. Doctor S believes that therapy A is superior to therapy B for condition C. Can Dr. S advise patient P with condition C to enroll in the randomized clinical trial without violating the ethical requirements of the personal care principle?

To that question I would answer "yes" if the randomized clinical trial has been justified according to the concept of clinical equipoise as constructed by Freedman (1987). "A state of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their less-favored treatment is preferred by colleagues whom they consider to be responsible and competent."

What about physicians who consider their colleagues either irresponsible or incompetent? What about physicians who feel they have special insights into the truth about therapies that are not shared within the clinical community? If their insights are based upon scientific evidence, they should present their evidence in an appropriate forum. If they are convinced that a randomized clinical trial is not justified, they should present evidence to support this belief to agencies having the authority to disapprove or terminate the randomized clinical trial.

Physicians are expected to conduct their practices and advise their patients according to standards established by and accepted within the clinical community. This community standard is designed to protect the public from deviant physicians who believe they have special insights into the truth about therapies. By definition, in a state of clinical equipoise, the community standard is that the relative merits of the therapies in such a state are not known.

Thus, a competent physician may, in many cases, offer to a patient an opportunity to consider participation in a randomized clinical trial comparing therapies A and B even though he or she believes A is superior to B without violating the personal care principle. When therapies A and B are in a state of clinical equipoise, the physician's belief regarding the superiority of A is to be distinguished from a "competent judgment."

Comment: Personal and Impersonal Care

Foster Lindley

INTRODUCTION

Doctor Royall has performed a distinctive service in canvassing the most important ethical considerations prompted by the practice of randomizing patients to different therapies in clinical trials. I agree with the thrust of his paper favoring nonrandomized clinical studies and will comment briefly on some of his arguments while adding my own. I am hoping that more reflection by investigators on why it is that chance is so important to them will make alternative procedures seem less threatening.

First, a personal note. I came upon James Ware's article "Therapies of Potentially Great Benefit: ECMO" in the November 1989 issue of this journal, by chance. I was so affected by what was said, as well as how it was said, that I could not complete it in a single sitting. If it had not been for the comments by Berry and Royall, thanks to the editorial format, I would have concluded that I simply misunderstood it. I did not realize that decisions regarding alternative statistical strategies, like decisions regarding alternative therapies, have themselves become matters of life and death. That people die in the service of abstract, controversial, statistical proofs, I cannot accept. That they die at the hands of physicians who mistakenly prefer one therapy to another, I can accept. Some will see an inconsistency there; I do not.

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ANY PARALLEL TRIAL IS IMPERSONAL

With the exception of the brief paragraph at the close, which I hope he will expand in his rejoinder, Royall's objection to the randomization principle is