In current practice, most clinical trials are designed to have early stopping rules. Furthermore, there is usually a team of investigators who are responsible for monitoring the studies to determine if an early stopping rule has been reached. Generally outcome results, except for toxicity, may not be reported in a publicly available interim report. Professor Royall believes that the intermediate results should be communicated to all participants as this will change their equipoise. It is a common experience that interim results may have wide fluctuations in outcome and should be regarded as preliminary until these clinical data has been carefully reviewed. The data on which these interim reports are based may not be reliable. Some trials are organized so that data is only submitted when there is an observed event. As a result, interim results may be seriously biased, as "bad news comes in first."

The ECMO trial by Bartlett et al. (1985) is an interesting study from many points of view. It is not clear if the critics of the study would have the same point of view if the results had turned out differently. The randomized consent or prerandomization design (Zelen, 1989b) was used in this trial. It was proposed in the late 1970s in order to make it feasible for more physicians to participate in randomized trials. Many physicians do not participate in clinical trials because they believe the physician-patient relationship would be compromised if they have to tell the patient about randomization. Essentially, the design consists of randomizing eligible patients to each treatment under study. If one of the treatments is best standard treatment, then it is not necessary to approach these patients for consent. Patients assigned to the experimental treatment are approached for consent. They are informed of the treatment they would receive in the trial. The federal regulations, in effect at that time, only required patient consent when they were departing from established and accepted methods. However, the code of federal regulations was subsequently changed to require consent whenever an individual is participating in any research activity. Consequently, it is now necessary to seek consent from all treatment groups. The investigators adopted the randomized consent design out of compassion for the parents. They felt it would be too difficult an experience to discuss both treatment options and were unwilling to give the experimental treatment outside of a clinical trial setting.

Finally, I wish to conclude my discussion by referring to Professor Royall's abstract. I completely agree with his suggestion that statistical scientists "work to improve the planning, execution and analysis of nonrandomized clinical studies." It would be interesting to learn about Professor Royall's suggestions. He did not elaborate on this point in the body of his paper. Although I believe that, whenever appropriate, randomized trials should be implemented, there are many situations where such trials are not feasible for both ethical and practical reasons. Unfortunately, many statisticians greet such proposals with some hostility. If we do not respond to this need, we will find clinicians seeking alternative ways of carrying out trials without the collaboration of statistical scientists.

Rejoinder

Richard M. Royall

The statistical debate about the ECMO study of Barlett et al. (1985) has focused on the small size of the control group, which in fact had only one patient, and at what level the results can be said to be statistically significant (Ware and Epstein, 1985; Wei, 1988; Begg, 1990). However there is another kind of unease with that study, unease that would have been *worsened* by the use of a larger randomized control group. It was my purpose in this paper to identify and explain the source of that unease. It is infringement of the personal care principle. In varying degrees, the same unease is a factor in virtually all randomized clinical trials.

My efforts to heighten statisticians' awareness of the personal care principle and the problems it poses for randomized choice of therapies should not be misconstructed as "attacking the ethics of RCTs" (as Professor Dupont puts it) or as another of those "... incessant attempts to replace [RCTs] with other forms of investigation" that require Dr. Byar's vigilance. Within limitations, proper informed consent procedures can resolve the clini-

cian-researcher's dilemma in many trials. If treatments are to be selected, not according to the physician's and patient's judgment about what is best for that patient, but by the toss of a coin, this change in the basis of decisions requires the patient's approval. Precise equipoise is a rare and fragile condition that is, fortunately, not required. What is required is that the physician be able, in good conscience and candor, to offer the patient the option of participating, and that the informed patient freely choose. The patient who elects to enter the trial then receives the satisfaction of helping in what he judges to be a worthwhile enterprise. On the other hand, if the physician cannot bring himself to make the offer or if sufficient numbers of patients do not agree, then researchers must indeed use methods other than the RCT to study the therapies in question.

Drs. Bartlett and Cornell give us a valuable look at the problems and frustrations of the clinician who would convince a skeptical world of the superiority of a radical innovation in therapy. It is noteworthy that they disagree with the popular emphasis on equipoise: "It is not necessary to have individual or institutional equipoise to design and conduct a valid clinical experiment."

Their insistence that "the Michigan ECMO trial was an experimental trial" seems to be based on a misunderstanding of what distinguishes experimental from demonstration trials. The critical elements are the belief and purpose of the participating clinician. If he is confident that one treatment is superior and his purpose is to demonstrate that superiority, then *for him* it is a demonstration trial. The possibility that the trial might prove him wrong is always there; if that possibility were the defining characteristic of an experimental trial, as Drs. Bartlett and Cornell assume, then it would be pointless to define "demonstration trials." The conflict with the personal care principle arises when a clinician participating in what is *for him* a demonstration trial assigns his patients to a therapy that he believes to be inferior.

In characterizing himself as the beleaguered defender of RCTs, Dr. Byar makes reference to Voltaire. Since I am certainly no enemy of RCTs I suggest that a more apt characterization might come from Cervantes, who gave us a hero known for his eagerness to do battle with opponents whose hostile intent was entirely imaginary. Unfortunately Dr. Byar's eagerness to do battle leads to serious misrepresentations and specious argument. In Section 2 he criticizes my choice of "the ECMO study" as an example, and writes "Curiously, Royall fails to point out that a previous issue of this very journal contained an article by Ware (1989) with eight sets of comments by other statisticians including Royall himself who found that study 'deeply disturbing'." Royall's failure might not seem so curious to one who realizes that there are *two different studies*, the one by Bartlett et al. (1985) in Michigan, which I used as an example in this paper, and a subsequent one by O'Rourke et al. (1989) in Massachusetts that Ware reported and on which I commented in *Statistical Science*.

I will not yield to the temptation to dispute each of Dr. Byar's comments that seems to me inaccurate or misleading, but one particularly frustrating instance deserves notice. In his Section 3 Dr. Byar writes: "Although Royall is clearly familiar with the need to avoid selection bias, he dismisses this point rather breezily by noting that statistical adjustment procedures can be used to remove any such biases even though he admits that this is not an option for unknown prognostic factors or for covariates on which we have no information." This is a gross and contentious misrepresentation of what I wrote in Section 3.1. I did not breezily dismiss selection bias, and I stated explicitly that one of the most important advantages of randomization is its tendency to provide balance on covariates for which statistical adjustments are impossible.

I did not imply that "all ethical problems in medical experiments will disappear as long as the physician... does what he thinks is in the patients' best interests" (Byar, Section 6). However I do question the prevailing emphâsis on randomization as a *sine qua non* that can put physicians (as it did Barlett et al.) in the position of acting *against* their better judgment regarding the patients' well-being.

Dr. Byar has a penchant for the false dichotomy: "Rather than always letting the physicians do what they think is best, it seems to me vastly preferable to encourage them to recognize the limitations of their knowledge and conduct randomized trials." Must we really choose between these two options? Surely it is possible *both* to recognize the physicians' *responsibility* to do what they think is best *and* to "encourage them to recognize the limitations of their knowledge and conduct randomized trials" when possible under informed consent. At the end of his Section 6, Dr. Byar manages to use this rhetorical device twice in a single sentence! There he asserts that "...a RCT is much more ethical... than for physicians stubbornly to deny uncertainty and do what they individually think is best... ." Is a physician's doing what he thinks is best not compatible with a candid acknowledge-

ment of uncertainty? Are all those who are using ECMO or some alternative therapy outside the context of a RCT guilty of stubbornly denying uncertainty? And in the final phrase of that sentence Dr. Byar implies that if one disagrees with his opinion then it follows that "one believes that ignorance is ethical." Non sequitur.

The personal care principle does not apply to the statistician, whose relationship to the patient in a clinical trial is quite different from the physician's. Professor Dupont's proposed *acceptable evidence principle* looks reasonable to me as a statistician, but it fails to acknowledge the physician's special relationship with one whom he has accepted as his patient. I might agree with Professor Dupont that "all lives have equal worth" but also recognize that the physician has specific responsibilities to his patient that are not at all analogous to his duties to those for whom he has not agreed to provide personal medical care.

There is a striking inconsistency between Professor Dupont's criticizing the idea that physicians may violate the personal care principle when required to do so by the law (e.g., reporting gunshot wounds) and his proposing that "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."

Professor Dupont's impression that "virtually all trials are demonstration trials at least in the psychological sense" accords with mine. It is remarkable that analysts routinely describe the absence of a treatment preference as an ethical prerequisite for enrolling patients in an RCT, while in fact many (if not "virtually all") trials are carried out by clinicians with a definite treatment preference.

I agree with Dr. Levine's first point, that the values of science are not distinct from those of ethics. The same ethical principles apply to the pursuit of knowledge that apply to other human activities. The problem faced by the physician-scientist is not a clash between ethics and science, but between the ethics of patient care and those of science; it is an ethical dilemma.

However I am not satisfied with Dr. Levine's representation of this ethical dilemma in terms of the general principles of beneficence, autonomy and justice. His analysis observes that the individual and society both have legitimate, potentially conflicting, interests that are grounded in the ethical principle of beneficence. The conflicts that arise are to be resolved through trade-offs and balances determined by our society's priorities. But according to the personal care principle, a patient's physician does not play the role of a judge who weighs both sides and determines trade-offs. He must serve his patient's interests. If the patient chooses to make a sacrifice on behalf of society, that is his decision to make, not his physician's.

The physician's responsibility to his patient is in important ways analogous to that of a lawyer to his client. A person in need of legal advice and assistance seeks an attorney who will agree to serve as *his* lawyer. The attorney who accepts the client incurs a duty to serve that client's legal interests. His proper actions in the case are not determined by weighing the interests of his client against those of others; they are entirely determined by the client's interests. ("The professional judgment of a lawyer should be exercised, within the bounds of the law, solely for the benefit of his client and free of conflicting influences and loyalties . . . "; *Code of Professional Responsibility*, American Bar Association.) The physician to whom a potential patient comes for medical advice and assistance incurs a similar fiduciary responsibility when he agrees to serve as that patient's physician (Fried, 1974, page 34).

With Dr. Levine's second conclusion, that "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," I disagree. In this situation the physician who believes that A is superior and prescribes its use is not guilty of violating community standards; the absence of a professional consensus has not prevented his making a judgment, nor does it render that judgment incompetent. Both Dr. Bartlett's preference for ECMO and a skeptic's preference for conventional therapy were, in 1984, competent judgments.

Dr. Levine's examples of physicians who have falsified eligibility criteria or advised patients to enroll in an RCT and withdraw if randomized to the "inferior" arm illustrate unethical behavior, to be sure. However, in such cases the question is not whether the physician's judgment about what is best for his patient is competent; it is whether his duty to his patient justifies dishonesty in dealing with others.

Professor Lindley illuminates another interesting facet of randomization: "Avoiding a sense of responsibility for difficult choices." It may be impossible to determine how strongly this aspect affects the decision to enroll a patient in a randomized clinical trial, but its ancient origins suggest a psychological force that should not be disregarded.

I thank Professor Lindley for pointing out the

NIH reprimand reported by Marwick (1990). A Boston hospital's Institutional Review Board was reprimanded for approving the use of a randomized consent procedure virtually identical to the one used in the Michigan ECMO study. It is encouraging that the widespread misgivings with this procedure have been so decisively affirmed.

Dr. Simes' discussion begins with a general view of the "trade-off between individual and community benefit." His arguments are, I believe, entirely valid from the perspective of those (statisticians, for example) not obliged by the personal care principle to serve the interests of specific patients. The real problem appears only when we consider the viewpoint of the physician whose patient is eligible for a randomized clinical trial. And when he turns to that viewpoint Dr. Simes appears to accept the personal care principle, acknowledging "... the ethical responsibility of physicians in keeping the patient's interests foremost in the doctor-patient relationship." Thus he agrees that a patient should not be randomized if the doctor considers one particular therapy to be in his better interests.

Although he accepts the personal care principle, Dr. Simes gives a series of caveats and examples that seem intended to illustrate its weaknesses or to limit its scope, so as to lessen the potential for its conflicting with randomized clinical trials. He makes the point that blind faith that the doctor's opinion is right is not desirable. But the personal care principle does not invite such blind faith; it simply provides a basis for reasonable confidence that the doctor's recommendation represents his honest opinion about what is best for the patient, not his need for more patients in one arm of an experiment.

Dr. Simes then observes that the physician's resources are limited, as is his ability to lay claim to community resources on behalf of his patients. That the physician must apportion his efforts among his own patients does not contradict the proposition that he has an obligation to those patients that supercedes his obligation to those with whom he has not entered into a doctor-patient relationship. And his inability to get both of his patients into the last available intensive care bed represents not so much a decision to do less than he can for a patient as an external limitation on how much he can do.

Likewise, a clinician who prefers a treatment that is available only in a randomized clinical trial must decide whether, in his judgment, participating in the trial represents a better course for his patient than whatever therapies are available outside the trial, and he must advise his patient accordingly. Again, there are external limitations on his options; within those limitations his patient's interests are of first importance.

Regarding Dr. Simes' discussion of demonstration trials, I think our differences are merely semantic. As I use the terms, experimental and demonstration trials are distinguished by the beliefs and objectives of the physician whose patient is entered. Dr. Simes describes a situation where a physician with a strong treatment preference organizes and assists in a trial in which he does not enter his patients, but colleagues who are in equipoise enter theirs. This is not a demonstration trial, in my sense of the term, and I see no conflict with the personal care principle.

Likewise, if regulatory authorities make a therapy available only through a randomized clinical trial, it might be entirely reasonable to call it a demonstration trial, but this is not the sense in which I used the term. A physician might properly judge that participation is in his patient's interest; the participant's failure to receive the favored therapy does not imply that his physician has failed to do his best.

I thank Professor Zelen for putting the ethical issues of RCTs in a broader perspective that includes Phase I and Phase II nonrandomized trials and for noting some general ethical problems that I did not address. I take exception to his assertion that "The only ethical distinction between randomized and nonrandomized trials is the patient consent process." I think there is a critical distinction to be made between a study where each patient's therapy is chosen on the basis of judgments (uncertain and fallible as all judgments are) about what is best for that patient and a study where the choice is made by a coin toss.

It must be acknowledged that cost considerations, policies on Medicare and Medicaid, etc., limit the physician's options in caring for patients. However, it is not clear that this means that the personal care principle is not operable, as Professor Zelen suggests. Within the constraints imposed on him, is not the physician still expected, by his patient and by society, to act in the best interests of that patient?

Does the personal care principle apply today to medical practice in the United States? I am not aware of a case in which a physician with an acknowledged preference for treatment A, and to whom both A and B are equally available, has been successfully sued for allowing a coin toss to lead him to prescribe B for a patient who is not autonomous, fully informed, and consenting to this

choice. But this might well be possible under current law of conflict of interest and of fiduciary relations. More to the point, many patients and physicians believe that physicians are supposed to honor the principle. As long as this is true, many randomized clinical trials, especially those involving children and others who are unable to give effective informed consent, will be problematic.

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