Comment: The Ethos of Clinical Trials

M. Zelen

Professor Royall is to be commended for his paper. He has brought together selected excerpts and ideas from the literature that remind us that there is an ethos associated with randomized clinical trials. However, before discussing the paper, it is worthwhile to put the paper and many of the ethical issues into a broader perspective.

The term ethics may be defined as the rules or standards governing the conduct of a profession. Another definition is that it refers to the moral quality of a course of action. Professor Royall, as well as others he has quoted, have sometimes used the term ethics to refer to both definitions. In my discussion I shall be concerned only with the latter definition. It is important to note that society's view of ethical behavior, in the context of a course of action, changes over time and will continue to change. Furthermore in many situations, ethics may vary with individuals, without either one being labeled as "unethical."

Any review of the literature of the ethics of clinical trials must cite the Belmont Report (National Commission, 1978a). This report has had perhaps the greatest influence during the last decade in influencing the thinking on the ethics of clinical trials. It puts forth three basic principles "that serve as a basic justification for the many particular ethical prescriptions and evaluations of human situations." These three ethical principles have been labeled: *Respect for Persons*, *Beneficence* and *Justice*.

Professor Royall's paper singles out randomized controlled trials (RCT) as an area of special concern with regard to ethical behavior. However, most clinical trials being conducted today are not RCTs. The bulk are Phase I and II studies. The customary usage of these terms is that Phase I trials are situations in which a treatment (usually a drug or drug combination) is to be used on humans for the first time. The object of the experiment is to find doses and schedules having acceptable toxicities. Phase II trials are generally concerned with attempting to find out if a treatment has any beneficial activity. Ideally, only when a Phase II trial results in benefit would a Phase III trial be initiated. A Phase III trial is defined to be a comparative trial in which experimental therapies are compared to best standard treatment or even with other experimental therapies. Phase I trials are never randomized; some Phase II trials may be randomized trials, but most of them are not randomized. Almost all Phase III trials are randomized, but some are carried out without randomization. It is clear in the context of the strategy of clinical investigations, that the Phase I and II studies must precede Phase III studies. It is not surprising that there are many more of these being conducted compared to RCTs.

Nearly all of the ethical concerns which Professor Royall directs at RCTs also hold for nonrandomized trials. Depending on the treatment, the nonrandomized trials may be either an "experimental" or a "demonstrative" trial. The equipoise argument must equally hold for nonrandomized trials. The problem of accumulating evidence as a trial proceeds, which can change a physician's subjective or objective assessment of a particular treatment, also apply to nonrandomized trials. Informed consent is required by the U.S. Code of Federal Regulations (1983) regardless of whether the trial is randomized or not. The physician must describe other available therapies, possible side effects and the patient's right to withdraw at any time. In view of the above observations, a paper on the ethics of RCTs is unnecessarily narrow.

The only ethical distinction between randomized and nonrandomized trials is in the patient consent process. In a conventional randomized trial, the patient cannot be informed of the actual treatment which will be given, but is told that the chosen treatment will be selected using a "chance" mechanism. Colloquially, the randomization is described as "tossing a coin" or allowing a "computer to choose the treatment." As a practical matter, randomized trials will involve a small number of treatments (at most four) as *all* of the therapies must be described to the patient at the time of informed consent. It should be noted that the practice of obtaining informed consent is not universally accepted in most countries of the world. Nearly

M. Zelen is Professor of Statistical Science, Department of Biostatistics, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115 and is Director, Division of Biostatistics and Epidemiology, Dana-Farber Cancer Institute, Harvard Medical School.

all developed countries do not require informed consent as we practice it in this country.

It would be worthwhile to note some general ethical problems which have not been addressed by Dr. Royall which apply to all clinical trials.

CHOICE OF PATIENTS

A fundamental ethical problem is the selection of the patient population to be chosen for the trial. Should the patient population be newly diagnosed patients or those that have failed to benefit from therapies that have been shown to be effective? Newly diagnosed patients represent the best patient material to evaluate a new therapy, but it would deprive patients from receiving therapies having proven benefit. Of course, this concern is not present when there is no therapy of proven benefit.

OUTCOME

If, in an ongoing clinical trial, a conclusion is reached that one of the therapies is beneficial, should the participating patients and their physician be immediately advised of the outcome (before publication)? Should consideration be given to changing the therapy program for patients not on the superior treatment?

EXPERIMENTAL THERAPY OUTSIDE OF TRIALS

Is it ethical for a physician to give an experimental therapy outside of a clinical trial? The federal regulations for protection of human subjects require informed consent whenever a systematic investigation is designed to develop or contribute to generalizable knowledge. Consent is not necessary if a physician gives an experimental therapy that is not part of an investigation. For example, if FDA approved drugs are to be used for disease conditions, other than those approved by the FDA, then it is not necessary to obtain patient's consent provided there is no research plan to evaluate the outcome. A similar situation holds if FDA approved drugs are used in new drug combinations or in different doses and/or schedules. As a result, many physicians do not participate in clinical trials, but still use experimental therapies. Unfortunately, they do not contribute data to the evaluation of these experimental therapies.

PAYMENT FOR RESEARCH

Studies sponsored by pharmaceutical companies often pay physicians for their participation. Physicians in private practice view these funds as income. The money does not represent income for physicians in academic medicine, but are used to supplement the resources available to carry out their research. The funds are supposed to be payment for the costs of carrying out the clinical trial, but invariably it more than covers costs. In the patient consent process, should the patient be informed about the transfer of funds, if the patient consents to enter the trial? One could regard the payment as a "bounty."

NUMBER OF TRIALS

The FDA requires that at least two clinical trials must be submitted for approval of a drug. Occasionally, this rule may be relaxed for ethical reasons. If a trial has shown the unambiguous superiority of a drug, it is difficult to envision situations where additional trials would be initiated to further test the drug.

Professor Royall argues that if a physician is to do "what is best for the patient" (personal care principle), then demonstration trials should not be done. In many clinical trials, what would be regarded as a demonstration trial by some physicians would be thought of as an experiment by others. Furthermore, it is quite possible that a physician's views could change over time for the same trial. It is too simplistic to label trials as experimental or demonstration. The experience of many senior clinical investigators is that early optimistic subjective views on experimental treatments are most often not confirmed in a controlled clinical trial. As a result, many senior clinical investigators believe it is unethical to prescribe a new treatment outside of a formal clinical trials setting. I would regard the personal care principle as desirable, but not operable. Patient care is heavily dictated by cost considerations. There is pressure from the federal government, through the Diagnostic Related Groups (DRG), to discharge medicare patients from hospitals as early as possible. At least one state (Oregon) is considering writing laws to limit Medicaid expense. The health insurance companies are continually challenging physician decisions. The physician can no longer exercise a personal care principle to all patients.

The alteration of equipoise as evidence accumulates in a clinical trial requires further comment. Most Phase III trials for chronic disease use survival (or some other time metric). Generally, the accrual period of a trial takes 2–4 years and an additional 2–5 years follow-up time to observe survival. As a result, it is not common to have very much outcome data while patients are being accrued to a study.

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-