Comment

R. John Simes

Richard Royall's paper illustrates well that the ethics of randomized trials remain controversial. He has shown that in advocating randomized trials some authors may have taken an overzealous stand on their use by stating that nonrandomized trials are worthless. Yet his own position is far too restrictive as to when randomized trials are ethical. A practice that prevents randomized trials from evaluating many therapies may deny patients access to optimal care and be even more unethical.

The potential trade-off between individual and community benefit is often ignored when randomized trials are advocated and this dilemma is well described by Royall in his paper. Nevertheless, such a conflict does not necessarily render randomization unethical, as I will discuss below. In this debate there are a number of important ethical principles to consider, none of which should assume overriding importance. Ethics from the perspective of the individual is the most important but not the solitary concern in clinical decisions.

STATISTICAL BASIS OF RANDOMIZED TRIALS

As Royall points out, the randomized trial is the most scientifically valid way of evaluating therapies. It ensures that there is no selection bias so that statistically significant differences between treatment groups can be attributed to the therapies rather than differences in the patient characteristics. Methods that adjust for known confounders or prognostic factors may lessen the impact of selection bias but cannot eliminate it. Two examples in cancer trials demonstrate graphically how nonrandomized comparisons of separate patient groups receiving the *same* therapy resulted in statistically significant differences in outcome, even after adjusting for known prognostic facts (Zelen, 1985).

The scientific value of randomized trials in determining optimal therapy is critical in this ethical debate. Randomized trials are more likely to identify the better treatment and, by being more credible within the medical community, more likely to influence clinical practice and hence improve clinical care. Hence, from the social utilitarian principle of maximizing the common good for present and future patients, anything less than randomized trials is unethical.

But what of the individual utilitarian principle of maximizing the good for an individual patient. We can all agree on the value of a trial which is "for the good of one and all." But what if it is for "the good of all, but one?" (Simes, 1990). In these circumstances, should randomized trials be abandoned? The argument that one treatment in a randomized trial may be slightly inferior than the other must be balanced against the alternative of generally inferior therapy in a world where randomized trials were not undertaken or severely restricted. Gilbert, McPeek and Mosteller (1977) have argued that ethics should look at participation in a system of trials rather than just an individual trial. Consider which of two societies we would wish to live in. Society A, where randomized trials ensure the best medical treatments available are used, albeit with the possibility of receiving a slightly inferior treatment as part of such a trial, or society B, where the treatment (mistakenly) believed to be the best is given but where medical therapies still used are considerably worse than any from society A.

INDIVIDUAL OR COMMUNITY ETHICS

Having considered these two perspectives, it is quite clear that the statistical basis of clinical trials (whether randomized or not) is implicitly based on the social utilitarian principle of maximizing community benefit. In determining the sample size for a clinical trial, decision theoretic models have been described which explicitly refer to a patient horizon (potential patients available to receive one or other treatment) and devise a strategy for maximizing the number of patients receiving the superior one. Classical methods also recognize the trade off between current and future patients by setting acceptable type I and II error rates. That is, the level at which we consider the case for the better treatment made (where we declare it "known" that one treatment is better) is based on consequences of an incorrect decision for future patients. Schwartz, Flamant and Lellouch (1980) make this even more explicit when planning sample size of pragmatic trials by suggesting the restriction of type III errors (where the inferior

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therapy is mistakenly recommended for future patients).

If the sole consideration is just the next patient, then there could be little ethical basis for any clinical trials, randomized or not. For most phase I or II studies, new therapies are piloted in nonrandomized trials with the hope that some of these may replace existing treatments. However, the overall results of these new treatments are usually disappointing with significant advances in the minority. Individual ethics would therefore argue for maintaining the status quo. Hence we should recognize that there is a possible trade-off between benefits to future patients at the expense of trial patients in most trials undertaken, both randomized and nonrandomized.

Royall is quite correct in pointing out that certain statistical methods do not remove this trade-off. Dynamic randomization rules, such as play-the-winner, or statistical procedures for early stopping of a trial simply reduce the number of patients in total assigned to the (eventually "known") inferior treatment. But some trade-off between conflicting ethical demands should be recognized.

Are there circumstances where in fact there is no trade-off, that is where *all* trial patients and future patients benefit? This indeed may be often the case. First, the level of uncertainty in any randomized trial should be sufficient to make any apparent differences only marginal. That is, in any ethical randomized trial the trade-off should be small enough to be of no practical significance (the condition Royall refers to as equipoise). Second, the treatment which eventually proves superior may only be available on the trial. This was the case with streptomycin for tuberculosis (Medical Research Council, 1948) and more recently for AZT for the treatment of AIDS. Third, as part of a clinical trial patients may receive a better level of overall care and monitoring of their progress than is given outside the trial protocol. While another ethical principle is to offer the same care to patients not taking part in the trial, there may be some benefits of trial participation that are an integral part of it.

A comparison of patients taking part in a randomized trial of adjuvant therapy for soft tissue sarcoma showed that the untreated controls in the *randomized trial* had a significantly better outcome than the *nonrandomized* untreated controls. This difference was statistically significant even after adjusting for known prognostics factors (Antman, 1983). Assuming this difference is not due to chance, there are only two possible explanations: either the patients received better care as part of a randomized trial protocol or there was selection bias not able to be accounted for by adjusting for known prognostic factors. In the former case, patients randomized on trial benefited from participation; in the latter, this nonrandomized trial would have produced erroneous conclusions.

THE PERSONAL CARE PRINCIPLE

In considering the ethics of randomized trials, it is essential to ensure the ethical responsibility of physicians in keeping the patient's interests foremost in the doctor-patient relationship. Hence Royall correctly states that patients should not be randomized on a clinical trial if the doctor considers one particular therapy to be in the better interests of the patient. Neither should the patient be randomized if the patient has a clear preference for either therapy. But this ethical principle should also allow for the doctor's opinion to consider *either therapy on a randomized trial* as in the patient's best interest. "Blind faith that no physician ever put another interest above the health of a patient" is clearly not desirable. Yet, blind faith that the doctor's opinion is right when good evidence of treatment benefit is lacking is even less desirable. There are countless examples throughout medical history where man put his faith in doctor's opinion only to be proved wrong in subsequent trials. (Bull, 1959; Lambert, 1978).

Royall suggests that the only circumstances when the doctor need depart from the personal care principle is when explicitly required by law or regulation. Yet it should be recognized that there are conflicting demands for individual patient care faced by doctors (to a varying degree) every day. These range from the simple demands on the doctor's time (should this consultation be extended at the expense of the next) to more difficult dilemmas such as the decision to admit one of two patients to the last available intensive care bed or the decision to prescribe expensive therapy of marginally greater benefit within a restricted hospital budget. In a world of limited resources, society already accepts the need for some trade-off between individual and community benefit. Individual ethics and the personal care principle must remain an extremely important but not overriding ethical principle. There is a need to strike the right balance.

EXPERIMENTAL AND DEMONSTRATION TRIALS

Royall is willing to accept the ethical justification for *experimental trials*, albeit under fairly limited circumstances when there is equipoise between

the two therapies under consideration. The circumstances under which such trials are justified, I believe, is considerably broader than he suggests. However, he also argues that for *demonstration trials*, aimed solely at convincing others of the value of a new therapy, they can never be justified. If such a trial were carried out by clinicians already convinced of the value of the new therapy and responsible for the individual care of trial patients, then I would have to agree. However, there are still at least two circumstances where demonstration trials can be ethically undertaken.

First, the trial organizers, having some belief in the value of a new therapy, could invite those clinicians, who are uncertain as to the better treatment, to take part in the randomized trial. This approach can be defended for each participating clinician using Royall's own principle of competence. If a competent clinician considers either therapy on the randomized trial the best available *in his or her judgement*, then he or she is acting ethically to randomize even if the trial organizers feel confident one particular treatment will eventually prove superior. This was essentially the case in ISIS-2, a placebo-controlled randomized trial of streptokinase and aspirin in patients with suspected acute myocardial infarction (ISIS-2 Collaborative Group, 1988). Streptokinase, a drug which dissolves the clot in the coronary artery, had already been suggested to be of value in reducing total mortality by a meta-analysis of randomized trials. Yet clinicians remained unconvinced and continued not to use this treatment, partly due to the concerns of bleeding complications. As further results came to light from other trials, the organizers continued to pass this information onto the clinical investigators but still left the decision as to which patients should be randomized to the individual doctor and patient. The results of the trial eventually demonstrated convincingly the value of this treatment in saving lives. This therapy's introduction was delayed for many years because a large-scale randomized trial had not been undertaken earlier. The community benefit of this trial is quite clear. Individual ethics are also maintained by involving doctors and patients in the trial who did not have a clear preference for either therapy.

The second circumstance in which demonstration trials are ethical is where government or regulatory authorities consider that the potentially superior therapy has still not been adequately evaluated. These authorities should rightly base their decision on protecting the welfare of the whole community and will delay the introduction of a new drug or technology until appropriate randomized trials have been undertaken. In these circumstances, participation in such a trial would also be ethical for clinicians who regard the new treatment as superior but are otherwise unable to give it to their patients.

CONCLUSIONS

The issue should no longer be whether it is ethical to undertake randomized clinical trials. The case for randomization has clearly been made. Rather, the issue should be whether the particular randomized trials undertaken are ethical. This requires the careful observance of ethical guidelines in their design and conduct and at all times ensuring that the importance of the individual is not lost sight of in the cause of science.