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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