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-