Rejoinder

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INTRODUCTION

The discussants have raised many important issues about the ECMO study and about clinical research in general. The diversity of views expressed about our study is not surprising, given the difficult issues that it raises. It is especially interesting that some of the discussants believe that no patients should have been randomized, while others think that randomization was stopped to quickly.

I do believe that some of Dr. Berry's comments do not address scientific issues, especially those that question the motivation of the investigators, suggest that we could not think independently about the strengths and weaknesses of alternative designs, or suggest that we would have knowingly given an inferior therapy to study patients. I will not address these comments. Instead, my reply focuses on the following points: 1) the role of randomization in medical research, 2) the ethical justification for randomization in the ECMO study, 3) randomized consent, 4) study design and 5) data analysis. Finally, I will comment on some of the lessons to be learned from this study and its reception.

THE ROLE OF RANDOMIZATION IN MEDICAL RESEARCH

Dr. Berry is very critical of the role of randomization in therapeutic research. He argues that it is both unethical and unnecessary; unethical because we always have some preference among treatments, and unnecessary because data banks and registry studies can provide equally valid information about the relative efficacy of therapies. Although others have taken Dr. Berry's position, most scientists now recognize the unique role of randomization in the conduct of experiments and clinical trials. It would not be useful to repeat the arguments in favor of randomization here (see, for example, Byar et al., 1976), but a few points deserve emphasis.

Biostatisticians and physicians involved in therapeutic research are accustomed to hearing reports of new therapies that give outstanding results in uncontrolled studies. Regrettably, only a small fraction of these new treatments prove to be superior to standard therapies when evaluated in a randomized trial. A distinguished expert in cancer clinical trials, Dr. Charles Moertel, spoke humorously to this point as keynote speaker at the 1980 meeting of the Society for Clinical Trials in a talk entitled "How to succeed in clinical trials without really trying." The key to the strategy was the use of nonrandomized studies to generate very favorable results. Similarly, early uncontrolled studies of coronary bypass surgery led to exaggerated claims about its efficacy in the treatment of coronary artery disease (Detre, 1984). Randomized trials showed that some patient groups benefited from bypass surgery, while others did as well with medical management. Dr. Moertel's message would apply equally well to research on many other medical conditions. It is important to be skeptical about 'breakthroughs' and to examine them carefully.

The limitations of observational studies arise from the natural heterogeneity of human response. Although predictors of patient outcome have been identified in many settings, these predictors usually explain a small part of the variability among patients or study participants. The Framingham Heart Study, for example, has played a central role in identifying several important risk factors for myocardial infarction (MI), but the high risk group identified by these risk factors has a 2-year probability of MI of only about .1 (Shurtleff, 1974). Our limited ability to predict outcome using quantitative methods creates the potential for bias in subjective methods of assigning patients to therapy. The high success rates sometimes reported from nonrandomized studies in high-risk diseases suggest that clinicians can identify patients with a favorable prognosis even when they cannot quantify their criteria.

It is important to recognize that Bayesians and frequentists agree about the purpose and value of randomization. Rubin (1978), for example, shows that, when the mechanisms that sample experimental units, assign treatments, and record data are not ignorable, the Bayesian must model them. The resulting inferences then become sensitive to model specification. Randomized trials can, of course, give misleading results, but randomization provides a framework for calculating error rates or posterior probabilities that do not depend on assumptions about comparability.

Dr. Berry argues that therapies could be evaluated by analyzing registry data gathered in large national data banks. This is unrealistic. Registries that do not include well-defined entry criteria, complete coverage of study populations, careful quality control procedures, and other features of careful research are of little value. Carefully designed and implemented registry studies have proven to be of value, for example in the study of coronary artery bypass surgery (Detre, 1984) and percutaneous transluminal coronary