Comment

Richard G. Cornell

The issues involved in the design of a clinical study of extracorporeal membrane oxygenation (ECMO) therapy for respiratory distress in newborn infants are clearly presented by Ware. He fully develops the reasons for the selection of an adaptive design, namely, the desire to minimize the number of patients on standard control therapy if in fact the new treatment, ECMO, is superior with respect to survival.

The adaptive design used in the randomization portion of the Michigan ECMO trial was a treatment selection procedure. Ware describes the Michigan experience in detail, but one aspect of that study is omitted. The plan developed before the study began included provision for continuing the therapy selected during the randomization phase, with the same study entry criterion, in order to better estimate the rate of survival under the selected treatment.

As Ware notes, the stopping rule for the randomized portion of the Michigan trial was attained after only 10 patients were treated, one of whom was randomized to conventional therapy and died, and 9 of whom were randomized to ECMO and survived. However, additional patients were admitted to the study for treatment with ECMO without randomization. Cornell, Landenberger and Bartlett (1986) reported 19 successes without any failures with ECMO. They calculated a lower one-sided 99% confidence limit for the probability of survival on ECMO, based on all 19 survivals, of 0.785.

Thus there was considerable evidence on the effectiveness of ECMO with respect to survival prior to the Harvard study, but, as Ware points out, the information on survival for patients on standard intensive therapy was not on concurrent controls except for one patient. Moreover, the historical information was not fully documented in the Michigan report. However, some background information on survival on standard therapy was obtained at Harvard. Ware reports that 11 out of 13 infants (85%) who met eligibility criterion for the study, but were seen in 1982 and 1983, died. This is similar to the historical death rate observed at Michigan prior to the study there.

Whether or not another trial with randomization to a control treatment as well as to ECMO was needed after the Michigan study is open to debate. Yet it is clear from Ware's description that ethical and scientific concerns were fully considered in the design of the Harvard study. Like the Michigan study, the Harvard study began with randomization to both ECMO and control treatments and provided for a switch to a single therapy once sufficient data accumulated. The switch was made based on a prespecified number of deaths in either treatment group in the Harvard study, instead of on the basis of reaching a prespecified number of results favorable to one of the treatments as in the Michigan study. Thus the Harvard design provided for adequate comparison of ECMO and control treatments to assure protection against a type I error, while the Michigan design provided for a low expected number of patients on the inferior treatment. Both studies had a high probability of selecting the best treatment if one was markedly superior to the other.

Later Cornell (1987) reported that over 100 infants had been treated with ECMO at the University of Michigan with a success rate over 80% and that an ECMO central registry had also been established with an overall survival rate of 78.2% among 614 infants. During 1986 the survival rate for the registry was 81.7% among 263 infants. These rates were well above the survival rate observed for conventional therapy in the past and provided strong evidence that the choice of ECMO as the better treatment for survival was appropriate. Toomasian et al. (1988) updated the ECMO registry information to 715 cases with a survival rate of 81 percent. They also provided information for separate diagnostic categories and potential risk factors.

Another adaptive design which, like that described by Ware, does guard against a type I error, has been proposed by Cornell (1987). This design is an extension of the urn design proposed by Wei and Durham (1978) upon which the Michigan ECMO study was based. Either the stopping rule for randomization suggested by Wei and Durham, or by Ware, could be used.

Cornell proposed taking u large, where u is the number of balls of each type in the urn initially. The two types of balls correspond to a new treatment of potentially great benefit and a control with a well established low survival rate. With a large u, early allocation probabilities for treatment and control would be nearly equal regardless of the results with the first patients entered. This would be similar to

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the equal allocation probabilities used initially in the Harvard study.

Cornell also presented an expression which accelerates the divergence of the allocation probabilities as the results in favor of one of the treatments becomes more pronounced. It is a function of the number of balls of each type in the urn and has the allocation formula of Wei and Durham for simple random selection as a special case. Acceleration would tend to compensate for a large initial value of u in terms of its effect on the expected number of patients allocated to the inferior treatment. It is this acceleration feature which distinguishes Cornell's proposal and makes it a viable alternative to the design presented by Ware and used in the Harvard ECMO trial.

The last suggestion made by Cornell concerns rejection of the null hypothesis of equal success probabilities on the control and the new treatment when more balls for the new treatment are added to the urn. A balls is added to the urn for one type of treatment whenever success is obtained on that treatment, or failure on the other. Cornell proposed that the null hypothesis be rejected only if the number of balls added for the new treatment exceeds that for the control to the extent that the posterior probability of correct selection, denoted by PPCS and conditional on observed frequencies, is high. This along with selection of a large value of u would enable the results of a randomized-play-winner trials to be used for hypothesis testing as well as for treatment selection.

An analysis based upon the PPCS would apply for any adaptive randomization scheme that depends only on the observed results without knowledge of the identity of the two treatments. It is a posterior probability in that it conditions on the observed allocations and frequencies of success on the two treatments. It is not a posterior probability in the sense of Bayesian inference, but is a function of the success probabilities under the control and new treatment.

The formula for PPCS could be used to evaluate the power of an RPW trial after completion of the experiment by substitution of the null and minimum alternative values of success probabilities. It could also be used to calculate an empirical significance level by substitution of the null and maximum indifference values of success probabilities. The approaches to analysis described by Ware would also be appropriate.

Although the accelerated convergence feature of this alternative design is attractive, detailed procedures for specifying u, the acceleration parameter, and the rule for discontinuance of randomization have not been developed. Neither has it been compared with the design presented by Ware. His design for the Harvard ECMO study meets the need for an adaptive design which responds to ethical considerations, yet provides adequate protection against an erroneous conclusion.

In closing I commend Professor Ware for the sensitivity to ethical issues and attention to scientific rigor which he has displayed in his work on the evaluation of the ECMO procedure. His discussion of statistical issues raised by the study will be especially helpful to anyone considering an adaptive design in a similar critical situation in the future.

ADDITIONAL REFERENCES

CORNELL, R. G. (1987). Play-the-winner in pediatrics: The ECMO trial. *ASA Proc. Biopharmaceutical Section* 243–245.

TOOMASIAN, J. M., SNEDECOR, S. M., CORNELL, R. G., CILLEY, R. E. and BARTLETT, R. H. (1988). National experience with extracorporeal membrane oxygenation for newborn respiratory failure: Data from 715 cases. *ASAIO Trans.* **34** 140–147.

Comment: Recent Progress in Clinical Trial Designs That Adapt for Ethical Purposes

Janis Hardwick

1. INTRODUCTION

Controlled medical trials are conducted for a variety of reasons, but in general the desire to validate new treatments that will, overall, decrease the suffering of the afflicted motivates their use. One classical and accepted approach to controlled research is the randomized clinical trial (RCT) in which patients are allocated randomly to competing therapies in such a way that an approximately equal number of patients is assigned to each regimen. But, as the current controversy illustrates, disparity often exists between the environment assumed necessary for a formal scientific inquiry and that of many real-life research situations.

The conflict between the need to conduct research and the desire to attend to the needs of individual

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