Comment

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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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