Comment

D. Y. Lin and L. J. Wei

As always, it is our great pleasure to read Professor Ware's paper. We appreciate the opportunity to discuss this interesting and well-written article. As far as we know, the Boston ECMO study was the second well-documented trial which used an adaptive design, the first one being the Michigan ECMO study. We regard this work of Professor Ware and his medical colleagues as a very important contribution to the area of clinical trials.

Although various data-dependent treatment assignment rules have been studied for the past three decades, their applications to medical trials are rather limited. As discussed in Professor Ware's paper, most adaptive designs are deterministic and may introduce bias into the study. In the Boston ECMO trial, after the randomization ceased, it soon became evident to the medical investigators that patients were all receiving ECMO. This led Professor Ware to suspect that sicker babies were enrolled in the second phase of the study. Indeed, the patient group in this stage seemed different from that of the first stage. This kind of selection bias reduces the degree of significance of the ECMO effect. Another reason that investigators do not use adaptive designs is that the responses from the study patients are usually not instantaneous. Most data-dependent rules have very little value for such situations.

An interesting adaptive design, the randomized play-the-winner rule of Wei and Durham (1978), was used in the Michigan ECMO study. This rule is a randomized version of Zelen's play-the-winner rule and is applicable to the case where patients may have delayed responses. It is not deterministic and is less vulnerable to experimental bias than other adaptive designs. This design can be easily described with an urn model. An urn has balls of two different types which are marked A and B. We start with α balls of each type. When a patient enters the study, a ball is drawn at random and replaced. If it is type k, then treatment k is assigned to this patient, where $k = A, B$. When a response of a previous patient to treatment k occurs, we add β balls of type k to the urn if the response is a success. Otherwise, β balls of the other type are added to the urn. Let this rule be denoted by RPW(α, β). It can be shown that such designs tend to assign more patients to the better treatment.

The RPW(1, 1) design was used for the Michigan ECMO trial. Partly by chance and partly due to the early successes of the ECMO babies, only one baby was assigned to the conventional treatment. Hence, the Michigan study did not provide sufficient concurrent experience with both regimens. Bartlett et al. (1985) concluded in retrospect that it might have been better to use a RPW(3, 1) design. A RPW(α, β) with $\alpha \geq 3$ gives high probability of having several early subjects on both treatment arms. Similarly, the permuted block design employed in the first phase of the Boston study ensured that there would be sufficient numbers of patients in both groups.

After conducting clinical trials with adaptive designs, it is important to know how to analyze this kind of data. For a Bayesian or other believer in the likelihood principle, the assignment and the stopping rules used for the trial will be ignored in the analysis. However, it is less clear how to analyze these data from a frequentist point of view. Wei, Smythe, Lin and Park (1990) studied a number of inference procedures under the RPW(α, β) design. Their exact methods can be modified to accommodate other adaptive designs, even those including early termination such as the one used in the Boston study. Furthermore, their asymptotic procedures can be applied to other adaptive designs with mild constraints.

Dr. Ware reported a profile likelihood confidence interval for the difference Δ between the survival rates of ECMO and CMT. Such an approximate interval is obtained by inverting the likelihood ratio statistic for testing $\Delta = \Delta_0$. Therefore, a profile likelihood confidence interval is genuinely *two-sided*. The 95% one-sided interval (0.131, 1) reported by Professor Ware was actually based on the 90% two-sided interval (0.131, 0.626). Other two-sided profile intervals with different confidence coefficients are shown in our Table 1.

Wei, Smythe, Lin and Park (1990) show that the profile likelihood intervals perform well for a RPW design with sample size more than 50. However, a design with both adaptive and sequential features was used in the Boston trial, and it is not clear to us if these large-sample procedures are appropriate or not. To this end, a small simulation study was conducted with the present design. Since Dr. Ware's design is an

D. Y. Lin is a Postdoctoral Research Fellow, Department of Biostatistics, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115. L. J. Wei is Professor, Department of Statistics, University of Wisconsin, 1210 West Dayton Street, Madison, Wisconsin 53706.