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

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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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