Foreword

This volume is a collection of the papers presented at the week long Conference on Adaptive Designs held at Mt. Holyoke College in the summer of 1992. Professors Steve Durham, Nancy Flournoy, Gordon Simons, and Michael Woodroofe should be congratulated on organizing such a successful conference. It was deemed advantageous to publish these excellent papers in a single volume rather than have them published separately in a variety of statistical journals. All the papers have been critically reviewed.

The scientific community widely regards the randomized clinical trial with a 50-50 treatment allocation rule as the "gold standard" for generating scientific evidence to evaluate two competing regimens. However, there has been an ongoing ethical concern with regard to the implementation of such trials. The principal ethical issue is that about half of the patients on a randomized clinical trial receive an inferior treatment. This has motivated statistical scientists to develop new methods for planning clinical trials. The two main directions of this research have been to: (i) develop early stopping rules so that a trial can be terminated early with the possibility of reducing the overall number of patients on a randomized clinical trial; and (ii) develop methods which make use of the accruing outcome data that allow changing the treatment allocation rule during the course of the trial. In a broad sense, (i) is a special case of (ii).

The area of research in (ii) is referred to as "adaptive clinical trials" and is one of the main topics of this volume. The principal idea is, during the course of the study, to allocate proportionally fewer patients to treatments which appears to be accruing less favorable endpoint information. The desirability of utilizing an adaptive allocation scheme is especially appealing in studies where the major response variable has a clear cut definition of success and/or failure and can be observed without long follow-up time. For example, in a recent trial to evaluate the drug AZT in reducing the risk of maternal-infant HIV transmission, a 50-50 randomization scheme was utilized to allocate 239 pregnant women to the AZT group and 238 mothers to the placebo group from April 1991 through December 1993. The endpoint for the study is either the newborn being HIV positive or negative. Although it may take more than 24 weeks after the birth to safely claim that an infant is HIV negative, a positive HIV infant can be accurately identified within

12 weeks. At the end of this study, there were 60 HIV positive infants in the placebo group, but only 20 in the AZT group (see Connor, Sperling, Gelber, Kiselev, Scott, O'Sullivan, VanDyke, Bey, Shearer, Jacobson, Jiminez, O'Neill, Bazin, Delfraissy, Clunane, Coombs, Elkins, Moye, Stratton, and Balsley, 1994). The setup of this study appears to be ideal for an adaptive clinical trial. If the treatment assignments had been done with the randomized play the winner rule (Zelen, 1969; Wei and Durham, 1978), on average, 360 and 117 of the mothers would be in the AZT and placebo groups, respectively, and only 60 (instead of 80) infants would be HIV positive. With the random treatment allocations actually used in the study, a 95 percent confidence interval for the difference of the transmission rates between the placebo and AZT groups is (11 %, 23%). With the randomized play the winner rule, the corresponding interval would be (9%, 25%), which has very little loss of efficiency.

Studies in which the major endpoint information requires a relatively long time to evaluate may not be suitable for using adaptive designs. However, even for such trials, one may use adaptive designs based on a relatively quick intermediate response (or surrogate marker). The statisticians at Eli Lilly and Company conducted a trial using this interesting approach (see Tamura, Faries, Andersen, and Heiligenstein, 1994). An alternative approach is to use a multi-stage adaptive design. That is, at each each interim analysis, if it is decided that the study should be continued, proportions of future patients assigning to the two groups before the next interim look are determined by a summary statistic based on the major endpoint, which does not have to be a dichotomous response.

Physicians generally have no problem with the usage of the adaptive design, which in fact coincides with the philosophy of their medical practice. On the other hand, some clinical investigators, statisticians and federal agencies may feel uncomfortable to use anything other than the gold standard. A well-conducted adaptive clinical trial will provide an unbiased assessment on the relative merit of the two treatments. Although an adaptive design is usually more complex than a conventional randomized clinical trial, with the widespread availability of computing and the automation of clinical trial data collection systems, in our opinion, the use of adaptive designs will grow in the future.

Although most statistical issues on adaptive designs have been extensively discussed in the literature, many challenging theoretical and practical problems remain to be solved. A few important ones are tack-

led and elegant solutions are presented in this volume. Some interesting and practically useful procedures for searching the "optimal" dose in Phase I/II studies are also proposed, as well as applications to reliability and quality control. We hope that the collection of papers in this volume will accelerate both the theory and practice of this important area of research.

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