OPTIMAL GROUP SEQUENTIAL DESIGNS FOR THE ANSCOMBE–COLTON MODEL

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Optimal group sequential designs are obtained for both the original and a truncated version of a selection model formulation of the problem of designing a clinical trial to compare two treatments. These optimal designs can be described as decision boundaries prescribed by nominal significance levels which vary dramatically, becoming less stringent as additional information becomes available. The corresponding Bayes risks indicate the magnitude of the penalty incurred due to both the restriction to group sequential designs and the imposition of varying degrees of truncation, and provide the baseline against which to assess the performance of the different types of group sequential designs that appear to be most commonly used in practice. Increasing the number of groups results in substantial improvements in the performance of the optimal designs, unless the point of truncation is quite small relative to the number of patients whose treatment will be determined by the results of the trial. In the latter circumstances, there is little to be gained through the choice of design; the primary design characteristic is the size of the trial. This result emphasizes the critical importance of planning clinical trials to be of adequate size. Our findings indicate conclusions concerning optimal group sequential designs which differ from those obtained within the usual hypothesis-testing framework and hence have implications for the general problem of designing such comparative clinical trials.

1. Introduction

In long-term clinical trials with sequential patient entry, strict application of fixed sample size designs is unjustified on ethical grounds but it is often argued that fully sequential designs are impractical due to the need for continuous assessment of the accumulating data; this might be particularly difficult to organize in the case of complex, multicenter trials. In such trials it is common practice to assess the accumulating data repeatedly at regularly spaced intervals of time. The planned use of group sequential designs has gained wide acceptance as a convenient approach to the challenge of monitoring such trials.

The problem of designing a clinical trial to compare two treatments usually is addressed from the hypothesis-testing point of view. As the two treatments are considered to be on a more-or-less equal footing, a three-decision formulation of the problem is most common: the null hypothesis of no difference is to be tested against each of two possible alternatives, typically symmetrically located around the null. Control of the error probabilities at the null and specified alternatives is the primary requirement and different designs are compared on the basis of expected sample sizes.

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