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Graphical Search for Two-Stage Designs for Phase II Clinical Trials

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ABSTRACT: In a typical two-stage design employed in a phase II cancer clinical trial for efficacy screening, a fixed number of patients are initially enrolled. The trial may be terminated for lack of clinical efficacy of treatment if the observed number of treatment successes after the first stage is too small. Otherwise, an additional fixed number of patients are enrolled to accumulate additional information on efficacy. Simon's optimal design and minimax design have often been applied to designing phase II clinical trials. Other designs have largely been ignored. In this paper, we introduce a graphical method to search for a good design that is a compromise between the optimal and the minimax designs. *Control Clin Trials* 2001;22:367–372 © Elsevier Science Inc. 2001

KEY WORDS: *Minimax design, optimal design, early stopping*

INTRODUCTION

Suppose we want to carry out a phase II clinical trial to determine whether a new cancer therapy has sufficient efficacy for further consideration by clinical investigation. For ethical and economic reasons, most clinical trials are required to be designed as multi-stage experiments, and the most popular number of stages for phase II cancer clinical trials has been two. A two-stage trial can be described as follows: At stage 1, n_1 patients will be treated. If the number of responders is not larger than the lower boundary r_1, the trial is terminated for lack of treatment efficacy. Otherwise, an additional n_2 patients will be treated. If the accumulated number of responders is not larger than the lower boundary r, the trial concludes that the therapy lacks sufficient efficacy. Otherwise, the new therapy will be considered for further study. We may also employ an upper boundary to stop the trial early when a significantly high efficacy is observed from stage 1, but we consider only early stopping in case of lack of efficacy in this paper.

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Received September 8, 2000; accepted March 26, 2001.

Controlled Clinical Trials 22:367–372 (2001)

655 Avenue of the Americas, New York, NY 10010

0197-2456/01/$–see front matter
PII S0197-2456(01)00142-8

A two-stage design is defined by the number of patients to be accrued at each stage (n_1 and n_2) and the boundary values at stages 1 and 2 (r_1 and r). Let p_0 denote the maximum unacceptable probability of response and p_1 denote the minimum acceptable probability of response ($p_0 < p_1$). Suppose we want a design guaranteeing type I error probability α (i.e., the probability that we accept the therapy when its true response probability is p_0) and power of 1—β (or type II error probability β, i.e., the probability that we accept the therapy when its true response probability is p_1). There are many designs satisfying the requirement of type I and II error probabilities. Simon proposes two approaches to finding a good design among them [1]. The first, leading to the minimax design, is to minimize the maximum number of patients, $n = n_1 + n_2$. The second, leading to the optimal design, is to minimize the expected number of patients (EN) when the true response probability is p_0.

In planning a trial, we usually choose one of Simon's two designs by comparing the EN and n. Sometimes, however, the comparison may not be so clear, especially when the optimal design has a much smaller EN but a much larger n than the minimax design. For example, when $p_0 = 0.1$ and $p_1 = 0.3$, Simon's designs for (α,β) = (0.05,0.15) are given as (r_1/n_1,r/n) = (2/18,5/27) by the minimax criterion and (1/11,6/35) by the optimality criterion. The minimax design requires eight fewer patients in n than the optimal design, but the latter has a smaller EN (18.3) than the former (20.4) by over two. If the maximum number of patients we can accrue for the trial is at most 27, then we may want to choose the minimax design. Otherwise, however, we can find a good alternative in this case, if we search the designs between the minimax and optimal designs. The design (r_1/n_1,r/n) = (1/13,5/28) requires only one more patient in n than the minimax design, and its EN is very comparable to that of the optimal design (18.7 versus 18.3). Hence this design can be a good compromise between Simon's two designs.

In this paper, we propose to visually display candidate designs between the minimax and the optimal designs. As input variables, we specify N, the maximum number of patients we can accrue for a study, together with (p_0,p_1,α,β). The optimal design in our display will minimize EN among the designs with $n \leqslant N$. If N is smaller than the minimax design, then it will display no designs. If N is large enough, then our optimal design will be Simon's optimal design. The display will help us compare the minimax design and the optimal design and search for good alternatives to them.

SIMON'S TWO-STAGE DESIGNS

We use the notations in Simon [1]. Let $b(x;p,m)$ and $B(x;p,m)$ be the probability mass function and the cumulative distribution function for the binomial distribution with probability success p and number of trials m. Let p denote the true response rate of a new therapy. Suppose we want to test H_0: $p = p_0$ against H_1: $p = p_1$ ($p_0 \leqslant p_1$) with type I error probability α and power $1 - \beta$. For a two-stage design (r_1/n_1,r/n), the probability of accepting (more accurately, not rejecting) H_0 is given as

$$R(p) = B(r_1;p,n_1) + \sum_{x=r_1+1}^{\min(n_1,r)} b(x;p,n_1)B(r-x;p,n_2),$$

and the constraint on type I error probability and power is expressed as $R(p_0) \geq 1 - \alpha$ and $R(p_1) \leq \beta$.

Given (p_0,p_1), there are many designs satisfying a type I and II error probability constraint (α,β). Among them, Simon's minimax design minimizes the maximum number of patients n. On the other hand, Simon's optimal design minimizes the expected sample size when $p = p_0$ given as

$$\text{EN} = \text{PET} \times n_1 + (1 - \text{PET}) \times n,$$

where $\text{PET} = B(r_1;p_0,n_1)$ is the probability of early termination after stage 1 when $p = p_0$. The search for the optimal design proceeds as follows: for each n and each n_1 $(= 1, \ldots, n - 1)$, find the integer values r_1 and r that satisfy (α,β) constraint and minimize EN. We can save computing time by using the fact that as boundary values r_1 and r increase, type I error probability decreases and type II error probability increases.

To visualize the search procedure, we plot the minimal EN for each n $(\leq N)$. In this case, EN is the expected number of patients under $p = p_0$ for the optimal design among the designs requiring maximum number of patients n. The plot will start from the minimax design and end at $n = N$, and the optimal design will be the one with the minimum EN value within this range.

ALTERNATIVE DESIGNS

Usually we set N at a reasonable number we can accrue during the projected study period. Then, our search program goes through all n between that of the minimax design and N, and the design minimizing EN within this range of n will be located and marked as "optimal" in the plot. If N is large enough, then this local optimal design will be the same as Simon's optimal design. We will refer to the local optimal design as optimal in our paper whether it is the same as Simon's optimal design or not. We demonstrate how to use our plot to find a good design under some example settings.

Example 1: $(p_0,p_1,\alpha,\beta) = (0.4,0.6,0.05,0.1)$, $N = 60$

A plot of EN under this setting is given in Figure 1. Compared to the minimax design $(r_1/n_1,r/n) = (12/29,27/54)$, the optimal design $(r_1/n_1,r/n) = (14/31,29/59)$ does not save much in EN (38.06 versus 37.14). Hence we may choose the minimax design to save five $(59 - 54)$ patients in n. Not shown in Figure 2, Simon's optimal design, $(r_1/n_1,r/n) = (11/25,32/66)$, with EN = 35.98 requires 12 $(66 - 54)$ patients more in n to save EN by only about two. Our graphical program provides specification of a design such as n_1, r_1, n, r, PET, EN, and type I and II error probabilities when the circle representing the design is clicked. Figure 1 displays the specification of the minimax design that will appear when the corresponding circle is clicked.

Example 2: $(p_0,p_1,\alpha,\beta) = (0.1,0.3,0.05,0.15)$, $N = 35$

This example has been discussed in the Introduction section, and Figure 2 displays a plot of EN against n under this setting. The minimax design is given as $(r_1/n_1,r/n) = (2/18,5/27)$ and the optimal design is given as $(1/11,6/35)$.

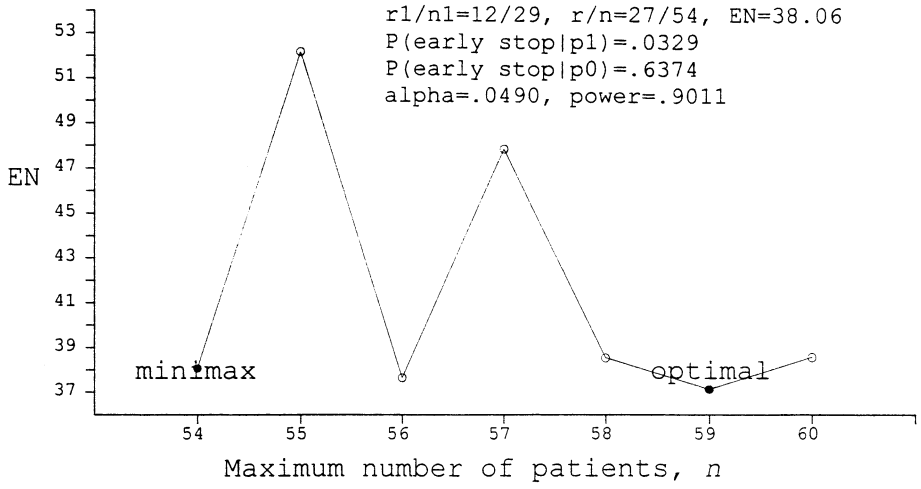

Figure 1 Two-stage designs for $(p_0,p_1,\alpha,\beta) = (0.4,0.6,0.05,0.1)$ with $N = 60$ and the specifications of the optimal design $(r_1/n_1,r/n) = (14/31,29/59)$ displayed.

The minimax design requires eight fewer patients in n than the optimal design, but the latter (EN = 18.3) has a smaller EN than the former (EN = 20.4) by over two. The design $(r_1/n_1,r/n) = (1/13,5/28)$ requires only one more patient in n than the minimax design, and its EN is very comparable to that of the optimal design (18.7 versus 18.3). Hence, it may be a good compromise between the minimax design and the optimal design, which is also Simon's optimal design.

Example 3: $(p_0,p_1,\alpha,\beta) = (0.3,0.5,0.05,0.15)$, $N = 55$

A plot of EN under this setting is given in Figure 3. The minimax design $(r_1/n_1,r/n) = (14/37,17/42)$ has EN = 37.56, whereas the optimal design $(r_1/n_1,r/n) = (7/21,19/48)$ has EN = 28.48. The minimax design requires over nine

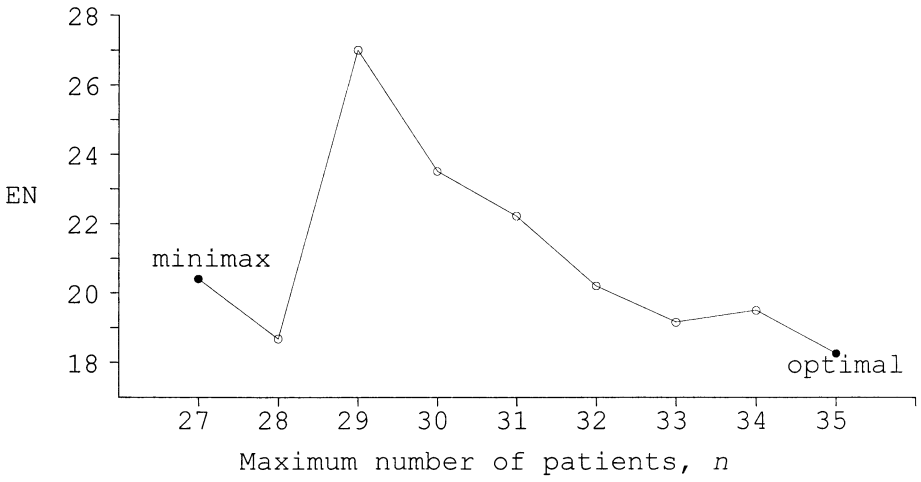

Figure 2 Two-stage designs for $(p_0,p_1,\alpha,\beta) = (0.1,0.3,0.05,0.15)$ with $N = 40$.

more EN than the optimal design. The design $(r_1/n_1,r/n) = (4/15,18/45)$ achieves an EN = 29.54 very close to that of the optimal design while saving three (48 − 45) patients in n. With $N = 55$, the optimal design is also Simon's design. Note that there is no design with $n = 43$ satisfying the (α,β) restriction.

DISCUSSION

In designing a two-stage phase II trial in patients with cancer, we usually choose either the optimal design or the minimax design by Simon, while ignoring those in between. Although the minimax and optimality criteria are statistically justified, neither may give us a satisfactory and practical design in a typical phase II trial. Very often, we can find a design between the minimax design and the optimal design that has n close to that of the minimax design and EN close to that of the optimal design. Because of the discreteness of the phase II designs (i.e., n_1, n, r_1, and r), some ns may have many candidate designs satisfying the type I and II error criteria, while some others have only a few or even none (see Example 3), especially for the small ns between the minimax and the optimal designs. This makes EN quite variable for small ns and the designs by the two criteria very disparate. In this case, we usually can find a design that has n very close to that of the minimax design and EN very close to that of the optimal design.

In this paper, we propose a procedure to find a compromise design satisfying these two criteria. In our procedure, we find a compromise design that has a minimal EN for each n by inspecting the plot of En against n for the "best" designs at different values of n. By specifying the maximum feasible number of patients N, we can determine the best compromise within the range of n for the minimax design and N.

As is mentioned by Simon, if the primary endpoint of a study is toxicity, not efficacy, then we can use the same design algorithm specified in terms of nontoxicity probability [1]. Our discussion has been limited to two-stage designs with lower stopping boundaries only. However, our graphical method can be

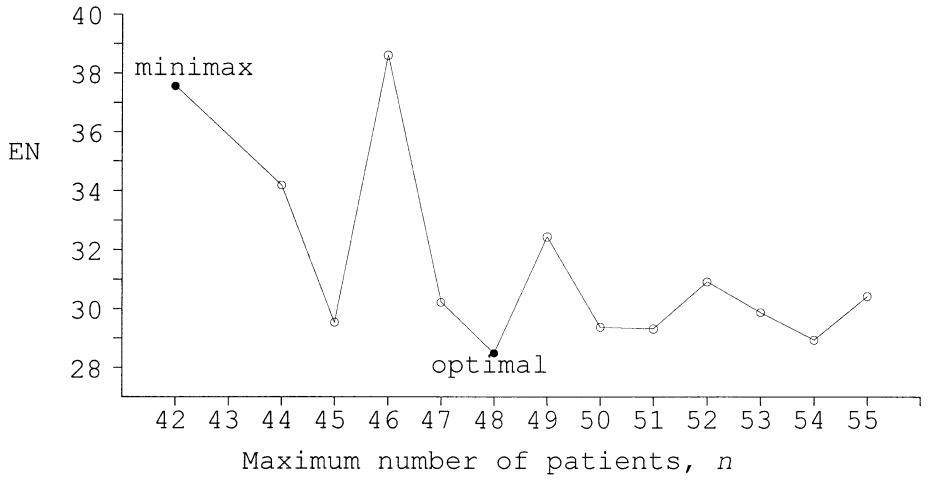

Figure 3 Two-stage designs for $(p_0,p_1,\alpha,\beta) = (0.3,0.5,0.05,0.15)$ with $N = 55$.

also applied to designs with only upper boundaries or both types of boundaries with any number of stages [2–4].

The program in C++ on Windows platforms is available from the second author upon request. A simpler program without the clicking capability to identify designs is available on the web at <<http://biostat.hitchcock.org/BSR/Analytics/OptimalMinimax.asp>>.

This work was partially supported by the grant R01-CA52733 from the National Institutes of Health, DHHS.

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