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Exact Operating Characteristics for Single-arm  
Phase II Trials

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# Exact operating characteristics for single-arm Phase II trials

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## 1 Introduction

Simulation is usually necessary to find the operating characteristics of clinical trials. We can get so used to relying on simulation that we use it when exact calculations would not be difficult. For a single-arm clinical trial with a binary response, the probabilities of reaching each of the stopping boundaries can be computed exactly without much effort. The resulting software will orders of magnitude faster than software that relies on simulation.

Suppose a trial has stopping boundaries of the form  $0/b_0, 1/b_1, 2/b_2 \dots$  where these rules mean to stop a trial early and reject an experimental treatment if there are no responses out of the first  $b_0$  patients, or if there is only one response out of the first  $b_1$  patients, and so on. For example, a rule may say to stop if there have been no successes out of the first  $b_0 = 4$  patients, or if there has been only 1 success out the first  $b_1 = 11$  patients, or only 2 successes out of the first  $b_2 = 17$  patients, etc. This note will show how to compute the probability of reaching each stopping boundary given a probability of response  $p$ . Note that it makes no difference what design gave rise to the boundaries. For example, the boundaries could have come from a Simon two-stage frequentist design [1], a Thall-Simon design based on random inequalities [2], or a design based on Bayes factors [3].

## 2 Algorithm

Let  $p$  be the true probability of a success on an experimental treatment. For a maximum sample size of  $n$ , let  $M$  be the  $n + 1$  by  $n + 1$  matrix such that  $M_{i,j}$  is the probability of having observed  $i$  successes after treating the  $j$ th patient. Note that the indices of this matrix run from 0 to  $n$ . We now discuss how to compute the entries of  $M$ .

Note that  $M_{0,0} = 1$  because we are certain to have observed no successes until after we have treated at least one patient.

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We cannot have observed more successes than the number of patients we have treated, and so  $M_{i,j} = 0$  if  $i > j$ . In other words,  $M$  is upper-triangular.

$M_{0,j} = (1 - p)^j$  if  $j \leq b_0$  where  $b_0$  is the maximum number of patients that can be treated with no successes.

There are two possible ways to treat the  $j$ th patient and have observed  $i$  successes. One is to have observed  $i$  successes after  $j - 1$  patients, continue to treat the next patient, and the  $j$ th patient fails. Continuing to treat the  $j$ th patient means that  $M_{i,j-1}$  was not on a stopping boundary. The second possibility is to have observed  $i - 1$  successes after  $j - 1$  patients, continue to treat the  $j$ th patient, and observe a success. Continuing on to the  $j$ th patient via the latter route requires that  $M_{i-1,j-1}$  was not on a stopping boundary.

Define

$$s_j = \sum_{i=0}^n M_{i,j}.$$

This gives the probability of treating the  $j$ th patient. The probability of stopping after the  $j$ th patient is  $s_j - s_{j-1}$ . Since  $s_j$  is constant between stopping boundaries, it only needs to be computed at the boundaries.

The following algorithm will fill in the matrix  $M$ .

*Initialize  $M$  to zero*

```
for  $j = 0 \dots n$ 
  for  $i = 1 \dots n$ 
     $M_{i,j} = 0$ 
```

*Fill in the top row of  $M$*

```
for  $j = 0 \dots b_0$ 
   $M_{0,j} = (1 - p)^j$ 
```

*Fill in  $M$  below top row by columns*

```
for  $j = 1 \dots n$ 
  for  $i = 1 \dots j$ 
    if (the pair  $(i, j-1)$  is not a stopping boundary)
       $M_{i,j} += (1 - p)M_{i,j-1}$ 
    if (the pair  $(i-1, j-1)$  is not a stopping boundary)
       $M_{i,j} += pM_{i-1,j-1}$ 
```

The function for determining whether  $(i, j)$  is a stopping boundary returns true if and only if  $i$  is a valid boundary index and  $b_i = j$ .

Software implementing this algorithm is available from the author on request.

### 3 A note on Simon two-stage designs

The stopping boundaries for a Simon two-stage are often given as two pairs of numbers. For example, consider a trial to test the null hypothesis of a 20% response rate against an alternative rate of 40% with 0.05 type I error and 0.20 type II error. The stopping boundaries for this trial are 3/13 and 12/43. Such a trial would treat a total of 43 patients and stop early if there are 3 or fewer responses out of the first 13 patients. The trial will reject the experimental treatment if there are 12 or fewer responses at the end of the trial.

While there are nominally only two stopping boundaries, there are actually 13 stopping boundaries. If the trial treats 10 patients with no successes, there would be no point in continuing because the trial will stop even if the next three patients are successes. So the trial would actually stop for 0 out of 10 successes, 1 out of 11, 2 out of 12, and 3 out of 13. Similarly, the trial would stop early if there only 4 successes out of the first 35 patients because the trial would still reject if the remaining 8 patients responded favorably. The remaining boundaries are 5/36, . . . , 11/42, 12/43.

### References

- [1] Simon, R. (1989) Optimzal Two-Stage Designs for Phase II Clinical Trials *Controlled Clinical Trials*, 10, 1-10.
- [2] Thall, P. and Simon, R. (1994). A Bayesian approach to establishing sample size and monitoring criteria for phase II clinical trials. *Controlled Clinical Trials*, 15, 463-481.
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