Paper SD09

A SAS Macro to Design Phase II Clinical Trials

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ABSTRACT

This paper describes a macro, written by the author, which can assist in the design of Phase II trials. For study parameters provided by the user, the macro will generate a number of trial designs satisfying the user's requirements and produce a Word file, datasets, and graphs giving their properties.

INTRODUCTION

Phase II trials are a common form of medical research. They are generally of short duration and involve 30 – 50 patients. Their purpose is to determine whether the treatment being tested provides sufficient benefit to be worthy of further study. At the conclusion of a Phase II trial, an investigator (or drug company) decides whether the results warrant further study of the treatment. Such further study will usually be in the form of a more lengthy, and expensive, randomized comparative trial.

THE TWO-STAGE PHASE II CLINICAL TRIAL

Before a new drug is adopted for general use as therapy for a medical condition, it must undergo a series of studies to establish its benefit. One type of study is the Phase II clinical trial. A Phase II clinical trial is usually a single arm study whose primary purpose is to estimate the drug's efficacy and determine whether further investigations, perhaps randomized, comparative trial, are worthwhile.

Often the efficacy measure of interest is the response rate; i.e. the proportion of patients exhibiting a favorable response to the treatment. For a pre-determined sample size, n, and a positive integer b, the treatment is rejected if b or fewer of the n patients have a favorable response. Otherwise is considered worthy of further study. A two-stage plan includes an early stopping rule that calls for rejecting the treatment after n_0 (< n) patients if b_0 or fewer of the n_0 have favorable responses. Thus, such a clinical trial can be characterized by the four numbers b_0, n_0, b, and n where the treatment is rejected if b_0 or fewer of the first n_0 have favorable responses. Otherwise, the trial continues until n are accrued. We then reject the treatment if b or fewer of the n patients have favorable responses.

DESIRED PROPERTIES OF THE TRIAL

Let r_0 represent a poor response rate and r_1 represent a good response rate and PR(r) be the probability of rejecting a treatment whose true response rate is r. Then we would want $PR(r_0)$ to be large (perhaps ≥ 0.9) and $PR(r_1)$ to be small (perhaps ≤ 0.05). The analytic task is to determine, for given values or r_0 and r_1, a specific design having these desired characteristics.

FORMULAS FOR PROBABILITIES

Let r_0 and r_1 be fixed, let $1 - \alpha$ be the minimal acceptable value for $PR(r_0)$, and β be the maximum acceptable value for $PR(r_1)$. Let Binom(b, n, r) be the binomial probability of exactly b responses in n patients given a response rate r. Then

$$1) PR(r) = \sum_{i=0}^{b_0} Binom(i, n_0, r) + \sum_{i=b_0+1}^{n_0} [Binom(i, n_0, r) \sum_{j=0}^{b-i} Binom(j, n-n_0, r)]$$

and we want to assure that

2) $PR(r_0) \geq 1 - \alpha$ and

3) $PR(r_1) \leq \beta$

If the true response rate is r, then the number of patients needed for the study will be n_0 with probability PR(r) and n with probability 1 – PR(r). Thus the expected sample size, E(N) is a function of r given by

4) $E(N) = n_0 PR(r) + n[1 - PR(r)]$.

THE MACRO PHASEII

The macro, PhaseII, allows the user to specify r_0, r_1, α, β, and a minimum and maximum value of n. It performs a systematic search for values of b_0, n_0, b, and n satisfying 2) and 3) starting with the minimum value of n and increasing n by one until acceptable values are found. The macro restricts n to the interval [5, n/2] since early stopping rules requiring fewer than five or more than half the total sample size are usually undesirable. Also, if 2) and 3) are satisfied by a value of n, no larger values of n are considered.

If no design satisfying 2) and 3) is found, the macro reports that fact. Otherwise, it creates a WORD file, phase2.doc, describing all of the acceptable designs. This file is written in a way that allows the user to "cut and paste" the design preferred into a clinical protocol. The author is grateful for the contribution of Koen Vyverman whose macro, SAS2WORD, is used to convert the SAS output produced by PhaseII into a WORD file and who has graciously allowed me to use it in my macro. The macro also produces, for each acceptable design, a graph plotting both the early and overall rejection probabilities and the expected sample size as a function of the true response rate, r. Finally, for each acceptable design, a SAS dataset giving the design operating characteristics is produced.

These datasets are not printed, but are available to the user.

The macro is called by a statement of the form:

```
%phase2(r0 = , r1 =  , alpha =  ,  beta = , nmax
= , nmin =  );
```

EXAMPLE

Suppose we are asked to design a Phase II clinical trial of an experimental chemotherapy agent for a particular type of cancer. The investigator tells us that the standard treatment has a response rate of 40%. Hence, this response rate for the new agent would not be of interest. However, if this treatment has a response rate of 60%, we would want to study it further. The investigator is willing to accept a probability of 10% of rejecting the treatment if its response rate is 60% and is also willing to accept a probability of 10% of failing to reject the treatment if its response rate is 40%. He would like to have a maximum sample size of "around 40".

The macro, phase2 can be called by this statement:

```
%phase2(r0 = .4, r1 = .6, alpha = .10,  beta =
.10, nmax = 45, nmin = 25);
```

It happens that the investigator's requirements can be satisfied by a two-stage design with a maximum of 41 patients. In fact, there are 42 possible designs with a sample size of 41 patients. They have possible early stopping after the first 9 – 20 patients. Figure 1 shows the first part of the WORD file that is produced. Figure 2 shows one of the 42 graphs produced.

CONCLUSION

the design two-stage phase ii trials can be a daunting task, requiring a considerable amount of computation in order to generate one having desired properties. Although there are tables and internet based programs that can produce an acceptable design, it might be useful to consider all designs satisfying certain criteria. The macro, phase2, presented here, allows the user to do that. The author will be happy to respond to email requests for the macro..

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Figure 1

List of Plans of Minimal Size Satisfying Criteria

Mininum Sample Size = 41

Plan #1
If, for the first 9 patients, we have 1 or fewer responses, we will stop. Otherwise, we will accrue a total of 41 patients. If 21 or more respond, we will decide that the treatment is good. Otherwise, we will decide that it is not good. If the true response rate is 0.4 , we will have a probability of .07 of stopping early and a probability of .90 of deciding that the treatment is no good. If the true response rate is 0.6 , we will have a probability of .00 of stopping early and a probability of .10 of deciding that the treatment is no good.

41 other plans follow

Figure 2