Chapter 120

Single-Stage Phase II Clinical Trials

Introduction

Phase II clinical trials determine whether a drug or regimen has sufficient activity against disease to warrant more extensive study and development. In a single-stage design, a single group of patients is studied. Usually, investigators will know the response rate of other drugs against the disease. Unless the current drug can be shown to be significantly more effective, its use will not be pursued.

This module finds designs that meet the error rate (alpha and beta) criterion and minimize the sample size when an exact test of proportions is used. The algorithm, discussed by A'Hern (2001), is an exact version of the algorithm of Fleming (1982).

Technical Details

Phase I clinical trials are designed to provide information about the maximum tolerated dose levels of a treatment. They consist of three to six patients at each dose level and provide little information about the effectiveness of the treatment.

Phase II trials obtain initial estimates of the degree of treatment activity. A patient's response may be measured by the decrease in the size of a tumor. For example, a patient may be considered to have responded to treatment if the tumor shrinks by 50% or more. There is no control group in these designs. Rather, the purpose of the trial is to determine if the drug shows enough activity against disease to warrant a full-scale, phase III clinical trial.

Let *P0* be the largest response proportion that, if true, clearly implies that the treatment does not warrant further study. *P0* is sometimes called the response rate of a poor treatment. For example, for a new anti-tumor drug, this may be set to 0.10.

Let *P1* be the smallest response proportion that, if true, clearly implies that the treatment does warrant further study. *P1* is sometimes called the response rate of a good treatment. For example, for a new anti-tumor drug, this may be set to 0.30.

A statistical test of hypothesis may be conducted to test the null hypothesis that $P \le P0$ versus the alternative hypothesis that $P \ge P1$ (P is the true proportion responding to the treatment in the population). Let α be the probability of rejecting the null hypothesis when it is true. Let β be the probability of rejecting the alternative hypothesis when it is true.

A single-stage phase II design can be represented by two numbers: *N* and *R*. *N* is the sample size. *R* is the critical value. If *R* or fewer responses occur in the *N* patients, the drug is rejected. The design is found by searching for the minimum value of *N* for which a value for *R* can be found such that the following two error rate constraints are met:

$$\Pr\left(reject|P0,R,N\right) \ge 1-\alpha$$

and

$$\Pr\left(reject|P1,R,N\right) \le \beta$$

Limiting the Range of the Search

Because of the discrete nature of the binomial distribution by which these error rates are calculated, there is no closed-formed solution and so a search among possible values of *N* must be conducted. In order to speed up the search, only values of *N* between 0.8*F* and 4*F* are considered. *F* is the sample size based on the normal approximation to the binomial, suggested by Fleming (1982).

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

Power and Alpha

Power

Power is the probability of rejecting the null hypothesis that the proportion responding to the treatment is less than or equal to *P0* when this hypothesis is false. That is, Power = Pr(rejecting $P \le P0|P \ge P1$).

Beta is the probability of not rejecting the hypothesis that the proportion responding to the treatment is less than or equal to *P0* when this hypothesis is false. That is, Beta = Pr(not rejecting $P \le P0|P \ge P1$).

The common range of power is 0.6 to 0.999 (Beta = 0.001 to 0.4). Popular values for power are 0.80 and 0.90 (Beta = 0.1 and 0.2).

Alpha

Alpha is the probability of rejecting the hypothesis that the proportion responding to the treatment is less than or equal to *P0* when this hypothesis is actually true. That is, Alpha = Pr(Rejecting $P \le P0 \mid P \le P0$).

The range of Alpha is 0.001 to 0.25. Popular values are 0.05 and 0.10.

Effect Size

P0 (Maximum Response Rate of a Poor Treatment)

Enter one or more response proportions of a poor drug. If the true proportion responding to the treatment is less than this amount, study of the treatment will not be recommended.

This value must be less than *P1* and greater than zero.

P1 (Minimum Response Rate of a Good Treatment)

Enter one or more response proportions of a good drug. If the true proportion responding to the treatment is greater than or equal to this amount, study of the treatment can be recommended.

This value must be greater than P0 and less than one.

Example 1 – Validation using A'Hern

A'Hern (2001) presents tables of sample sizes for various values of the design parameters. Setting alpha = 0.05, beta = 0.20, *P0* = 0.05, and *P1* = 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9, A'Hern finds the corresponding sampling plans to be (using the notation *R*+1/*N*) 14/169, 4/27, 3/14, 2/7, 2/5, 2/4, 2/4, 1/1, and 1/1. This would be set up as follows.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Single-Stage Phase II Clinical Trials** procedure window by expanding **Proportions**, then **One Proportion**, then clicking on **Multi-Stage Trials**, and then clicking on **Single-Stage Phase II Clinical Trials**. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Power	**0.80**
Alpha	**0.05**
P0	**0.05**
P1	**0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9**

Annotated Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Design for Testing H0: P ≤ P0 versus H1: P ≥ P1

P0	P1	Alpha	Beta	Cut-Off R + 1	N	Actual Alpha	Actual Beta
0.050	0.100	0.050	0.200	14	169	0.045	0.194
0.050	0.200	0.050	0.200	4	27	0.044	0.182
0.050	0.300	0.050	0.200	3	14	0.030	0.161
0.050	0.400	0.050	0.200	2	7	0.044	0.159
0.050	0.500	0.050	0.200	2	5	0.023	0.188
0.050	0.600	0.050	0.200	2	4	0.014	0.179
0.050	0.700	0.050	0.200	2	4	0.014	0.084
0.050	0.800	0.050	0.200	1	1	0.050	0.200
0.050	0.900	0.050	0.200	1	1	0.050	0.100

Report Definitions
P0 is the maximum response proportion of a poor drug.
P1 is the minimum response proportion of a good drug.
N is the sample size.
If the number of responses ≥ R+1, P0 is rejected.
If the number of responses ≤ R, P1 is rejected.
Alpha is the probability of rejecting that P ≤ P0 when this is true.
Beta is the probability of rejecting that P ≥ P1 when this is true.

Summary Statements
A study requires 169 subjects to decide whether the proportion responding, P, is less than or equal to 0.050 or greater than or equal to 0.100. If the number of responses is 14 or more, the hypothesis that P ≤ 0.050 is rejected with a target error rate of 0.050 and an actual error rate of 0.045. If the number of responses is 13 or less, the hypothesis that P ≥ 0.100 is rejected with a target error rate of 0.200 and an actual error rate of 0.194.

Note that the designs match those of A'Hern (2001) exactly.