

## Chapter 120

# Single-Stage Phase II Clinical Trials

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## 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).

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## 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  $P_0$  be the largest response proportion that, if true, clearly implies that the treatment does not warrant further study.  $P_0$  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  $P_1$  be the smallest response proportion that, if true, clearly implies that the treatment does warrant further study.  $P_1$  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  $P \leq P_0$  versus the alternative hypothesis that  $P \leq P_1$  ( $P$  is the true proportion responding to the treatment in the population). Let  $\alpha$  be the probability of rejecting the null hypothesis when it is true. Let  $\beta$  be the probability of rejecting the alternative hypothesis when it is true.

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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:

$$\Pr(\text{reject}|P_0, R, N) \geq 1 - \alpha$$

and

$$\Pr(\text{reject}|P_1, R, N) \geq \beta$$

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## 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-form 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  $0.8F$  and  $4F$  are considered.  $F$  is the sample size based on the normal approximation to the binomial, suggested by Fleming (1982).

## Example 1 – Validation using A’Hern (2001)

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

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

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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**

### Output

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

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

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Solve For: [Sample Size](#)

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P0	P1	Alpha	Beta	Cut-Off R + 1	N	Actual Alpha	Actual Beta
0.05	0.1	0.05	0.2	14	169	0.045	0.194
0.05	0.2	0.05	0.2	4	27	0.044	0.182
0.05	0.3	0.05	0.2	3	14	0.030	0.161
0.05	0.4	0.05	0.2	2	7	0.044	0.159
0.05	0.5	0.05	0.2	2	5	0.023	0.188
0.05	0.6	0.05	0.2	2	4	0.014	0.179
0.05	0.7	0.05	0.2	2	4	0.014	0.084
0.05	0.8	0.05	0.2	1	1	0.050	0.200
0.05	0.9	0.05	0.2	1	1	0.050	0.100

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P0            The maximum response proportion of a poor drug.  
 P1            The minimum response proportion of a good drug.  
 Alpha        The probability of rejecting that P ≤ P0 when this is true.  
 Beta         The probability of rejecting that P ≥ P1 when this is true.  
 Cut-Off R + 1    The hypothesis test cutoff value. If the number of responses ≥ R + 1, P0 is rejected. If the number of responses ≤ R, P0 is not rejected.  
 N             The sample size.

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**Summary Statements**

A single-stage phase II single-arm clinical trial design will be used to test whether the proportion responding ( $P$ ) warrants continuation to the next phase ( $H_0: P \leq 0.05$  versus  $H_1: P \geq 0.1$ ). For a Type I error rate of 0.05, a Type II error rate ( $1 - \text{Power}$ ) of 0.2, and a good treatment minimum response rate of 0.1, 169 subjects will be needed. If the number of responses is 14 or more, the hypothesis that  $P \leq 0.05$  is rejected. If the number of responses is 13 or less, the hypothesis that  $P \geq 0.1$  is rejected.

**Dropout-Inflated Sample Size**

Dropout Rate	Sample Size N	Dropout- Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	169	212	43
20%	27	34	7
20%	14	18	4
20%	7	9	2
20%	5	7	2
20%	4	5	1
20%	4	5	1
20%	1	2	1
20%	1	2	1

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N	The evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula $N' = N / (1 - DR)$ , with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. $D = N' - N$ .

**Dropout Summary Statements**

Anticipating a 20% dropout rate, 212 subjects should be enrolled to obtain a final sample size of 169 subjects.

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