

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 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 $P \geq P_1$ (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.

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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

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

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	
Power.....	0.80
Alpha.....	0.05
P0	0.05
P1	0.1 to 0.9 by 0.1

Output

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

Numeric Results									
Solve For: Sample Size									
Hypotheses: H0: P ≤ P0 versus H1: P ≥ P1									
Power		Sample Size N	Response Rate		Alpha		Beta		Hypothesis Rejection Cut-Off R + 1
Target	Actual		Maximum of a Poor Treatment P0	Minimum of a Good Treatment P1	Target	Actual	Target	Actual	
0.8	0.806	169	0.05	0.1	0.05	0.045	0.2	0.194	14
0.8	0.818	27	0.05	0.2	0.05	0.044	0.2	0.182	4
0.8	0.839	14	0.05	0.3	0.05	0.030	0.2	0.161	3
0.8	0.841	7	0.05	0.4	0.05	0.044	0.2	0.159	2
0.8	0.813	5	0.05	0.5	0.05	0.023	0.2	0.188	2
0.8	0.821	4	0.05	0.6	0.05	0.014	0.2	0.179	2
0.8	0.916	4	0.05	0.7	0.05	0.014	0.2	0.084	2
0.8	0.800	1	0.05	0.8	0.05	0.050	0.2	0.200	1
0.8	0.900	1	0.05	0.9	0.05	0.050	0.2	0.100	1

Power	The probability of rejecting the null hypothesis that the proportion responding (P) to the treatment is less than or equal to P0 when this hypothesis is false (when P = P1). Power = Pr(rejecting P ≤ P0 P ≥ P1).
Target Power	The power that is required.
Actual Power	The power that is achieved when the actual response proportion is P1.
N	The sample size that is necessary to meet the desired power and alpha goals.
P0	The maximum response proportion of a poor drug. If the true proportion responding to the treatment (drug) is less than this amount, study of the treatment will not be continued.
P1	The minimum response proportion of a good drug. If the true proportion responding to the treatment (drug) is greater than or equal to this amount, study of the treatment will be continued.

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Alpha	The probability of rejecting that $P \leq P_0$ when this is true. $\text{Alpha} = \text{Pr}(\text{Rejecting } P \leq P_0 \mid P \leq P_0)$.
Target Alpha	The alpha that is required.
Actual Alpha	The alpha that is achieved.
Beta	The type two error rate. $\text{Beta} = 1 - \text{Power}$.
Target Beta	The beta error rate that is required.
Actual Beta	The beta error rate that is achieved when the actual response proportion is P_1 .
$R + 1$	The hypothesis test cutoff value. If the number of responses $\geq (R + 1)$, P_0 is rejected. If the number of responses $\leq R$, P_0 is not rejected.

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 $N' = N / (1 - \text{DR})$, 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.

References

A'Hern, R. P. A. 2001. 'Sample size tables for exact single-stage phase II designs.' *Statistics in Medicine*, Volume 20, pages 859-866.
 Fleming, T. R. 1982. 'One-sample multiple testing procedure for Phase II clinical trials.' *Biometrics*, Volume 38, pages 143-151.

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