Chapter 357

Randomized Phase II Selection Designs for Binary Data (Simon)

Introduction

This module finds sample size and probability of correct selection of a one-way, randomized phase II (pilot) design in which the outcome variable is binary. Often called *pick-the winner* design, these designs are useful when the best of multiple promising treatments needs to be determined with a stated probability. The winning treatment will be studied further in a phase III trial. Such situations arise when multiple treatments are combined and when one or more of them includes multiple doses of a particular drug.

Technical Details

The formulas used in this procedure are presented in Simon, Wittes, and Ellenberg (1985).

Suppose we anticipate N_g subjects in each of G groups for a total of N subjects. Assume that subjects are allocated equally to each group. Let Y_{gj} be the binary response (0/1) of subject j in group g. The response is modeled by the model $Y_{gj} \sim Bernoulli(P_g)$. The study is analyzed by computing the mean of Y in each group, $\bar{y}_g$. The winning group is the group with the largest value of $\bar{y}_g$.

Note that the procedure does not use a significance test nor power. The only outcome is the champion group.

Sample Size

This procedure only requires the responses rates of two groups: the group with the worst response rate and the group with the best response rate. These response rates are P0 (worst) and P1 (best). The probability that the best treatment produces the highest observed response rate is

$$\Pr(Best) = \sum_{i=0}^{N_g} f(i)\left[1 - B\left(i; P1, N_g\right)\right] + \sum_{i=0}^{N_g} b\left(i; P1, N_g\right) \sum_{j=1}^{G-1} g(i,j)/(j+1)$$

where

$$f(i) = \left[B\left(i; P0, N_g\right)\right]^{G-1} - \left[B\left(i-1; P0, N_g\right)\right]^{G-1}$$

$$g(i,j) = \binom{G-1}{j} \left[b\left(i; P0, N_g\right)\right]^{j} \left[B\left(i-1; P0, N_g\right)\right]^{G-1-j}$$

Here $b(r;p,n)$ is the binomial probability mass function and $B(r;p,n)$ is the cumulative distribution function of the binomial with success parameter p. The function $\binom{n}{r}$ gives the number of combinations of *n* choose *r*.

Using this formula, a binary search can be conducted for the smallest group size N_g which achieves a stated probability of Pr($Best$).

Maximum Possible Sample Size

Gibbons, Olkin, and Sobel (1977) point out that there is a maximum group sample size possible for each combination of Pr(Best) and D = P1 – P0. This maximum occurs when P0 = 0.5 – D/2 and P1 = 0.5 + D/2.

Example 1 – Finding Sample Size

Suppose the sample sizes are wanted for a pick-the-winner design where *P0* = 0.2, *D* = 0.1 0.15 0.2, G = 3, and Pr(Best) = 0.90.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 procedure window. 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	
Solve For	**Sample Size**
Pr(Best) (Probability of Selecting Best Group)	**0.9**
G (Number of Groups)	**3**
P0 (Worst Response Rate among Groups)	**0.2**
Input Type	**Enter D = P1 - P0**
D (Max Response Rate Difference among Groups)	**0.1 0.15 0.2**

Annotated Output

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

Numeric Results

Numeric Results

Probability of Selecting Best Group		Sample Size				Response Rates		
Target Pr(Best)	Actual Pr(Best)	Groups G	Per Group Ni	Total N	Max Ni Nm	Worst P0	Best P1	Max Diff D
0.9	0.90142	3	93	279	124	0.2	0.30	0.10
0.9	0.90278	3	44	132	55	0.2	0.35	0.15
0.9	0.90369	3	26	78	31	0.2	0.40	0.20

Report Definitions

Target Prob is the target probability that the study correctly identifies either the best group, or, one of the best groups.
Actual Prob is the probability that the study correctly identifies either the best group, or, one of the best groups.
G is the number of groups (arms) in the design.
Ni is the sample size per group.
Total N is the total sample size of all groups. It is Ni × G.
Nm is the maximum per group sample size required to achieve Pr(Best) for any value of D. It is found by setting P0 = 0.5 - D/2, P1 = 0.5 + D/2, and solving for Ni.
P0 is the response proportion of the group with the worst (lowest) response proportion.
P1 is the response proportion of the group with the best (highest) response proportion.
D = P1 - P0 is the difference between the groups with the best and the worst response proportions.

References

Simon, R., Wittes, R.E., and Ellenberg, S.S. 1985. 'Randomized Phase II Clinical Trials'. Cancer Treatment Reports, Volume 69, No. 12, Pages 1375 - 1381.
Gibbons, J.D, Olkin, I., and Sobel, M. 1977. Selecting and Ordering Populations, A New Statistical Methodology. John Wiley & Sons. New York, New York.

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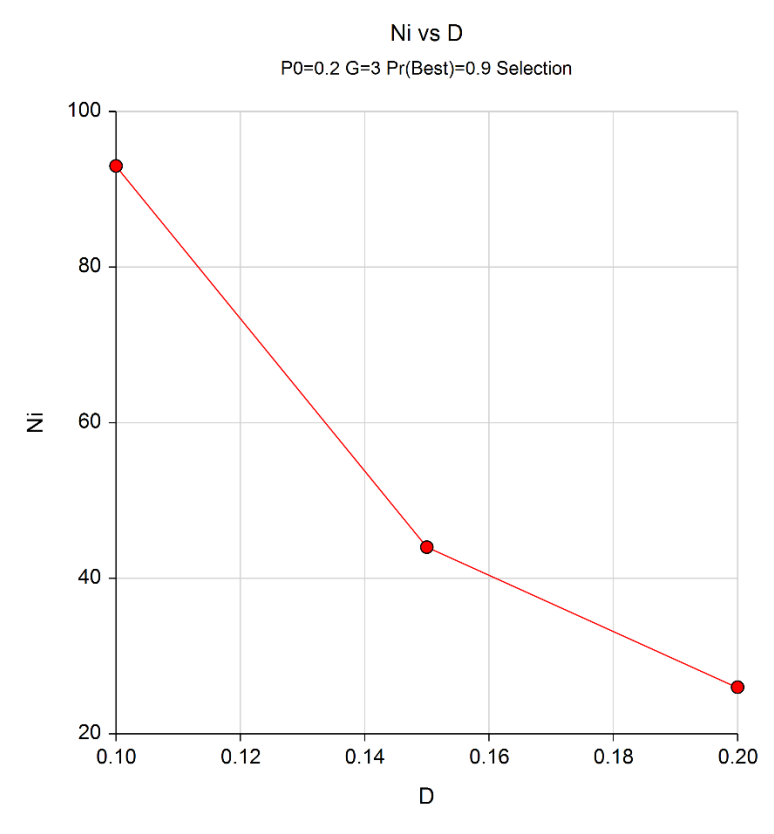
Summary Statements

A randomized phase II selection trial includes 3 groups with 93 subjects per group (a total of 279 subjects) attains a probability of selecting the best group of 0.90142. The study will produce binary outcomes. The response rate of the worst group is 0.2. The response rate of the best group is 0.3. The difference between these two groups is 0.1.

This report shows the results for the three cases.

Chart Section

Chart Section



The values from the Numeric Results report are displayed in this plot.

Example 2 – Validation using Simon *et al.* (1985)

Simon *et al.* (1985) page 1379 Table 3 presents sample sizes for several scenarios. We will use this table to validate this procedure. In this procedure *P0* = 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8; *D* = 0.15; G = 3; and Pr(Best) = 0.90. The resulting group sample sizes are 31, 44, 52, 55, 54, 49, 39, and 24.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Pr(Best) (Probability of Selecting Best Group)	**0.9**
G (Number of Groups)	**3**
P0 (Worst Response Rate among Groups)	**0.1 to 0.8 by 0.1**
Input Type	**Enter D = P1 - P0**
D (Max Response Rate Difference among Groups)	**0.15**

Output

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

Numeric Results

Numeric Results

Probability of Selecting Best Group		Sample Size				Response Rates		
Target Pr(Best)	Actual Pr(Best)	Groups G	Per Group Ni	Total N	Max Ni Nm	Worst P0	Best P1	Max Diff D
0.9	0.90256	3	31	93	55	0.1	0.25	0.15
0.9	0.90278	3	44	132	55	0.2	0.35	0.15
0.9	0.90228	3	52	156	55	0.3	0.45	0.15
0.9	0.90079	3	55	165	55	0.4	0.55	0.15
0.9	0.90078	3	54	162	55	0.5	0.65	0.15
0.9	0.90235	3	49	147	55	0.6	0.75	0.15
0.9	0.90318	3	39	117	55	0.7	0.85	0.15
0.9	0.90493	3	24	72	55	0.8	0.95	0.15

PASS has obtained the same group sample sizes. The procedure is validated.