Chapter 259

Bridging Study using a Non-Inferiority Test of Two Groups (Continuous Outcome)

Introduction

This procedure calculates the power and sample size required for bridging studies that use a non-inferiority test of the mean difference between the results for the two regions: original and bridging. Only a brief introduction to the subject will be given here. For a comprehensive discussion, refer to Liu, Hsueh, and Chen (2002).

Bridging Studies

Once a pharmaceutical product has been approved for use in one or more regions (countries) through a set of clinical trials, it is often desirable to register the product in a new region that was not included in the original study. When the cost and time needed to complete an additional set of clinical trials in the new region is prohibitive, a *bridging methodology* may be used to obtain the approval. The bridging analysis compares the results of a smaller and shorter *bridging study* in the new region with the data obtained in the original study.

The bridging analysis makes use of a two-group design in which the effectiveness in the new region is compared to the effectiveness in the original region using a non-inferiority test. The effectiveness in each region is measured by the difference between the means of a treatment group and a control group. The non-inferiority test shows that the differences in the two regions do not differ by more than a small amount, called the non-inferiority.

Test Statistics

This section summarizes the results found in Liu, Hsueh, and Chen (2002), page 974 - 976.

Original Study

Let Y_{ijk} be the clinical response of subject *k* on receiving treatment *j* in original study *i.* It is assumed that $i = 1, \ldots, I$. Also, *j* = T (treatment), C (control) and $k = 1, \ldots, N_{ij}$. Hence Y_{ijk} includes the response data from each of the original trials. Assume that the Y_{ijk} are independently normally distributed with means μ_{ij} and variance σ_{ij}^2. Further assume that μ_{ij} has a normal distribution with mean μ_{Oj} and variance γ_{Oj}^2. Hence, the $Y_{ijk}'s$ are independently normally distributed with mean μ_{Oj} and variance $\omega_{ij}^2 = \sigma_{ij}^2 + \gamma_{Oj}^2$.

Let Y_{ij} be the sample means. The MLE of μ_{Oj} is

$$t_{Oj} = \frac{\sum Y_{ij}/\left(w_{ij}^2/N_{ij}\right)}{\sum 1/\left(w_{ij}^2/N_{ij}\right)}, i = 1, \ldots, I; j = T, C$$

where

$$w_{ij}^2 = \sum \frac{\left(Y_{ijk} - t_{Oj}\right)^2}{N_{ij}}$$

is the MLE of ω_{ij}^2. The MLE's t_{Oj} and ω_{ij}^2 are solved for iteratively.

Bridging Study

Let Y_{Bjk} be the clinical response of subject *k* on receiving treatment *j* in the bridging study conducted in the new region. It is assumed that *j* = T, C and $k = 1, \ldots, N_{Bj}$. As before, the $Y_{Bjk}{}'s$ are independently normally distributed with mean μ_{Bj} and variance ω_{Bj}^2.

The MLE of μ_{Bj} is the sample mean Y_{Bj}. Let $t_{Bj} = Y_{Bj}, j = T, C$.

Non-Inferiority Test

The MLEs t_{Oj} and t_{Bj} are independently normally distributed with asymptotic variances estimated by

$$s_{Oj}^2 = \frac{1}{\sum 1/\left(w_{ij}^2/N_{ij}\right)}$$

and

$$s_{Bj}^2 = \sum \frac{\left(Y_{Bjk} - t_{Bj}\right)^2}{N_{Bj}^2}$$

Let $E_L = -NIM$ be the lower non-inferiority limit for the mean difference between regions, assuming $NIM > 0$. *NIM* is the non-inferiority margin. Often, *NIM* is set using $NIM = f(t_{OT} - t_{OC})$ where *f* is between 0 and 0.5.

The non-inferiority hypotheses, assuming higher values are better, are

$$H_0: \theta \leq -NIM \quad \text{vs.} \quad H_1: \theta > -NIM$$

where

$$\theta = (\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})$$

is the difference in treatment effects between the two regions.

The test statistic

$$t = (t_{BT} - t_{BC}) - (t_{OT} - t_{OC})$$

is an asymptotically unbiased estimate for θ.

The variance of t is given by

$$s^2 = s_{BT}^2 + s_{BC}^2 + s_{OT}^2 + s_{OC}^2.$$

The test statistic for the non-inferiority test is

$$T_L = \frac{(t + NIM)}{s}$$

The null hypothesis is rejected, and non-inferiority is concluded at significance level α if and only if $T_L > z_\alpha$, where z_α is the α^{th} upper percentile of the standard normal distribution. For a one-sided test such as this, α is often set to 0.025.

Power Calculation

Based on the above results, Liu *et al.* (2002) estimate the sample size required to meet the power, significance level, and effect size requirement as

$$N_B \geq \frac{A_1}{A_2 - A_3}$$

where

$$A_1 = \frac{\sigma_{BT}^2}{g_{BT}} + \frac{\sigma_{BC}^2}{1 - g_{BT}}$$

$$A_2 = \frac{NIM^2}{\left(z_\alpha + z_\beta\right)^2}$$

$$A_3 = s_{OT}^2 + s_{OC}^2$$

$$g_{BT} = \frac{N_{BT}}{N_B}$$

where $\beta = 1 - \mathrm{Power}$, σ_{BT}^2 is often estimated by s_{OT}^2, σ_{BC}^2 is often estimated by s_{OC}^2, and the actual difference between the two study differences is zero.

The power is obtained by rearranging this formula.

Example 1 – Finding Sample Size

A certain drug has been cleared for use in North America using parallel-group, treatment versus control clinical trials. These trials resulted in the following summary statistics:

$$N_{OT} = 973 \qquad \hat{\mu}_{OT} = 15.47 \qquad s_{OT} = 11.86$$
$$N_{OC} = 948 \qquad \hat{\mu}_{OC} = 4.14 \qquad s_{OC} = 10.39$$

Researchers in a region not included in the original study would like to register the new drug for use in that region. To do so, they are planning a bridging study with a significance level of 0.05 and a power of 0.8. They will set $\sigma_{BT} = s_{OT}$ and $\sigma_{BC} = s_{OC}$ .They want to calculate the necessary sample size when *f* is 0.2, 0.3, or 0.4. They are planning a balanced study.

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

Solve For	**Sample Size**
N_{OT} (Sample Size of Group OT)	**973**
N_{OC} (Sample Size of Group OC)	**948**
D_O (Mean Difference)	**11.33**
S_{OT} (Std Deviation of Group OT)	**11.86**
S_{OC} (Std Deviation of Group OC)	**10.39**
Power	**0.8**
Alpha	**0.025**
Group Allocation	**Equal (N_{BT} = N_{BC})**
Non-Inferiority Margin Input	**Enter f, the proportion NIM is of Do**
f (Proportion NIM is of Do)	**0.2 0.3 0.4**
σ_{BT} (Std Deviation of Group BT)	**11.86**
σ_{BC} (Std Deviation of Group BC)	**10.39**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Definition: $\theta = (\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})$
Hypotheses: H0: $\theta \leq -\text{NIM}$ vs. H1: $\theta > -\text{NIM}$
H1 Assumption: $\theta = 0$

Bridging Study									Original Study				
	Sample Size			Non-Inferiority		Standard Deviation			Sample Size			Standard Deviation	
Power	N_{BT}	N_{BC}	N_B	Proportion NIM is of Do f	Margin NIM	Treatment σ_{BT}	Control σ_{BC}	Alpha	N_{OT}	N_{OC}	Mean Difference Do	Treatment S_{OT}	Control S_{OC}
0.80031	629	629	1258	0.2	2.266	11.86	10.39	0.025	973	948	11.33	11.86	10.39
0.80021	205	205	410	0.3	3.399	11.86	10.39	0.025	973	948	11.33	11.86	10.39
0.80195	106	106	212	0.4	4.532	11.86	10.39	0.025	973	948	11.33	11.86	10.39

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N_{BT} The number of bridging study subjects assigned to the treatment group.
N_{BC} The number of bridging study subjects assigned to the control group.
N_B The total sample size of the bridging study.
f The proportion of |Do| used as the magnitude of the non-inferiority margin. NIM = f × |Do|.
NIM The magnitude of the non-inferiority margin. L = -NIM or U = NIM. NIM > 0.
σ_{BT} The response standard deviation of subjects assigned to the treatment group in the bridging study.
σ_{BC} The response standard deviation of subjects assigned to the control group in the bridging study.
Alpha The probability of rejecting a true null hypothesis.
N_{OT} The number of subjects assigned to the treatment group in the original study.
N_{OC} The number of subjects assigned to the control group in the original study.
D_O The difference between the group means (T - C) in the original study.
S_{OT} The response standard deviation of subjects assigned to the treatment group in the original study.
S_{OC} The response standard deviation of subjects assigned to the control group in the original study.

Summary Statements

A parallel two-group bridging study design will be used to test whether the bridging study mean difference (μ_{BT} - μ_{BC}) is non-inferior to the original study mean difference (μ_{OT} - μ_{OC}), with a difference non-inferiority proportion of 0.2 corresponding to a non-inferiority margin of 2.266 (H0: $\theta \leq -2.266$ versus H1: $\theta > -2.266$, where $\theta = (\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})$). The comparison will be made using a one-sided non-inferiority Z-test based on the difference in treatment effects of the two regions, with a Type I error rate (α) of 0.025. The group sample sizes of the original study were 973 (treatment) and 948 (control). The within-group standard deviations of the original study were 11.86 (treatment) and 10.39 (control). The original study mean difference (treatment minus control) was 11.33. The standard deviations within the treatment and control groups of the bridging study region are assumed to be 11.86 and 10.39, respectively. To detect a difference in treatment effects of 0 (or a bridging study region mean difference also of 11.33) with 80% power, the number of subjects needed for the bridging study will be 629 in the treatment group and 629 in the control group.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	NBT	NBC	NB	NBT'	NBC'	NB'	DT	DC	D
20%	629	629	1258	787	787	1574	158	158	316
20%	205	205	410	257	257	514	52	52	104
20%	106	106	212	133	133	266	27	27	54

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.

NBT, NBC, and NB — The evaluable sample sizes at which power is computed (as entered by the user). If NBT and NBC subjects are evaluated out of the NBT' and NBC' subjects that are enrolled in the study, the design will achieve the stated power.

NBT', NBC', and NB' — The number of subjects that should be enrolled in the study in order to obtain NBT, NBC, and NB evaluable subjects, based on the assumed dropout rate. NBT' and NBC' are calculated by inflating NBT and NBC using the formulas NBT' = NBT / (1 - DR) and NBC' = NBC / (1 - DR), with NBT' and NBC' 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.)

DT, DC, and D — The expected number of dropouts. DT = NBT' - NBT, DC = NBC' - NBC, and D = DT + DC.

Dropout Summary Statements

Anticipating a 20% dropout rate, 787 subjects should be enrolled in Group 1, and 787 in Group 2, to obtain final group sample sizes of 629 and 629, respectively.

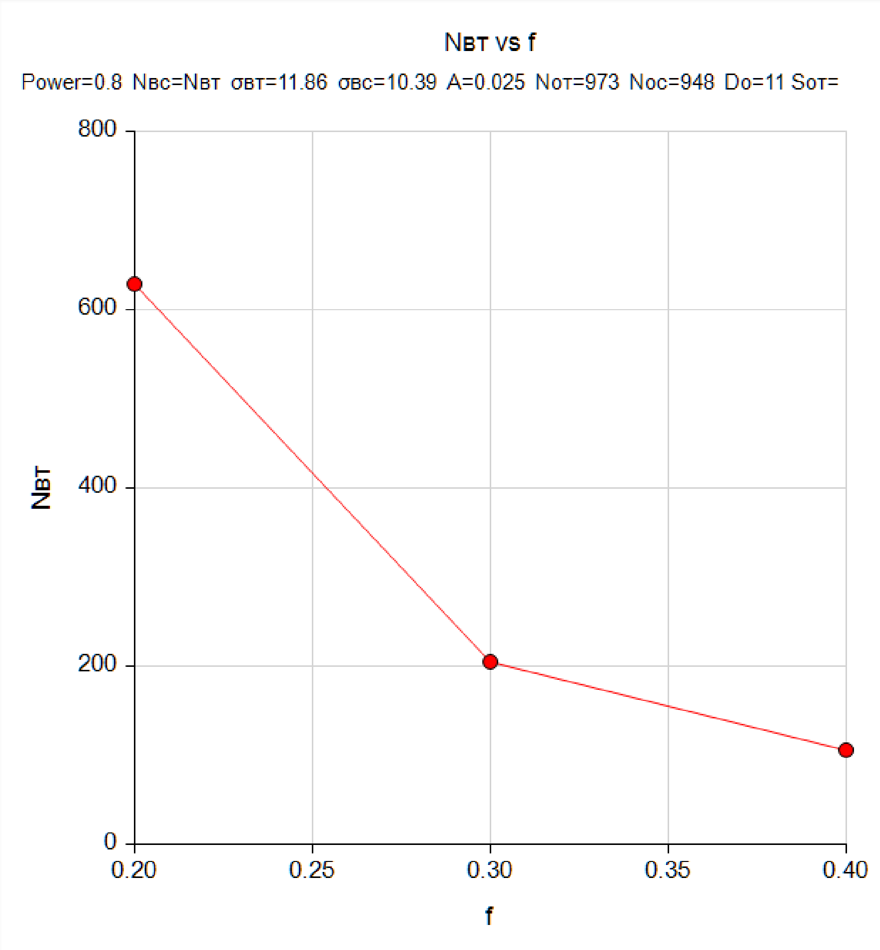
References

Liu, J.P., Hsueh, H., Chen, J.J. 2002. 'Sample Size Requirements for Evaluation of Bridging Evidence.' Biometrical Journal, Volume 44 (8), Pages 969-981.

This report shows the sample size for the indicated parameter configurations.

Plots Section

Plots



This plot shows the power versus the sample size. Note that we had to reduce the font size of the subtitle so that it would fit in the space allotted.

Example 2 – Validation using Liu et al. (2002)

Liu et al. (2002) include Table 2 of example results on page 977. We will use the entry from the sixth row and second column (f = 0.2) of this table as our validation example. The other table parameters are CV = 80%, $N_O = 1000$, $g_{NT} = 0.5$. They find the resulting bridging study sample size to be 55 per group (110 total).

These input values are consistent with the following summary statistics:

$$N_{OT} = 500 \qquad \hat{\mu}_{OT} = 4 \qquad s_{OT} = 0.8$$
$$N_{OC} = 500 \qquad \hat{\mu}_{OC} = 2 \qquad s_{OC} = 0.8$$

The significance level = 0.05 and the power = 0.8. Set $\sigma_{BT} = s_{OT}$ and $\sigma_{BC} = s_{OC}$.

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 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Sample Size**
N_{OT} (Sample Size of Group OT)	**500**
N_{OC} (Sample Size of Group OC)	**500**
D_O (Mean Difference)	**2**
S_{OT} (Std Deviation of Group OT)	**0.8**
S_{OC} (Std Deviation of Group OC)	**0.8**
Power	**0.8**
Alpha	**0.05**
Group Allocation	**Equal (N_{BT} = N_{BC})**
Non-Inferiority Margin Input	**Enter f, the proportion NIM is of Do**
f (Proportion NIM is of Do)	**0.2**
σ_{BT} (Std Deviation of Group BT)	**0.8**
σ_{BC} (Std Deviation of Group BC)	**0.8**

Output

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

Numeric Results

Solve For: Sample Size
Definition: $\theta = (\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})$
Hypotheses: H0: $\theta \le -NIM$ vs. H1: $\theta > -NIM$
H1 Assumption: $\theta = 0$

	Bridging Study								Original Study				
				Non-Inferiority		Standard Deviation			Sample Size			Standard Deviation	
	Sample Size			Proportion NIM is of Do	Margin	Treatment	Control				Mean Difference	Treatment	Control
Power	N_{BT}	N_{BC}	N_B	f	NIM	σ_{BT}	σ_{BC}	Alpha	N_{OT}	N_{OC}	Do	S_{OT}	S_{OC}
0.80063	55	55	110	0.2	0.4	0.8	0.8	0.05	500	500	2	0.8	0.8

PASS has also calculated a sample size of 55 per group, so the procedure is validated.