

Chapter 258

Bridging Study using the Equivalence Test of Two Groups (Continuous Outcome)

Introduction

This procedure calculates the power and sample size required for bridging studies that use an equivalence test to compare the efficacy of a treatment in two regions. The response data is continuous (assumed normal). Schuirmann's (1987) two one-sided tests (TOST) approach is used to test equivalence of a bridging study and the original study. 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 TOST equivalence test. The effectiveness in each region is measured by the difference between the means of a treatment group and a control group. The equivalence test shows that the differences in the two regions do not differ by more than a small amount, called the margin of equivalence.

Test Statistics

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

Original Study

Let Y_{ijk} be the clinical response of subject k on receiving treatment j in original study i . It is assumed that $i = 1, \dots, I$. Also, $j = T$ (treatment), C (control) and $k = 1, \dots, N_{ij}$. 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_{0j} and variance γ_{0j}^2 . Hence, the Y_{ijk} 's are independently normally distributed with mean μ_{0j} and variance $\omega_{ij}^2 = \sigma_{ij}^2 + \gamma_{0j}^2$.

Let \bar{Y}_{ij} be the sample means. The MLE of μ_{0j} is

$$t_{0j} = \frac{\sum Y_{ij} / (w_{ij}^2 / N_{ij})}{\sum 1 / (w_{ij}^2 / N_{ij})}, i = 1, \dots, I; j = T, C$$

Bridging Study using the Equivalence Test of Two Groups (Continuous Outcome)

where

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

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 $k = 1, \dots, N_{Bj}$. 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 $t_{Bj} = Y_{Bj}, j = T, C$.

Equivalence Test

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

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

and

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

Let $E_L = -E$ and $E_U = E$ be the lower and upper equivalence limits for the mean differences, assuming $E > 0$. Usually, E is set using $E = f(t_{oT} - t_{oC})$ where f is between 0 and 0.5.

The TOST equivalence hypotheses are

$$H_0: \theta \leq -E \text{ or } \theta \geq E \quad \text{vs.} \quad H_1: -E < \theta < E$$

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

$$s^2 = s_{BT}^2 + s_{BC}^2 + s_{oT}^2 + s_{oC}^2.$$

Bridging Study using the Equivalence Test of Two Groups (Continuous Outcome)

The two test statistics for the equivalence test are

$$T_L = \frac{(t + E)}{s} \quad \text{and} \quad T_U = \frac{(t - E)}{s}$$

The null hypothesis is rejected, and equivalence is concluded at significance level α if and only if $T_L > z_\alpha$ and $T_U < -z_\alpha$, where z_α is the α^{th} upper percentile of the standard normal distribution.

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

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

$$A_2 = \frac{E^2}{(z_\alpha + z_{\beta/2})^2}$$

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

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

where $\beta = 1 - \text{Power}$, 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:

$$\begin{aligned} N_{OT} &= 973 & \hat{\mu}_{OT} &= 15.47 & s_{OT} &= 11.86 \\ N_{OC} &= 948 & \hat{\mu}_{OC} &= 4.14 & s_{OC} &= 10.39 \end{aligned}$$

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
Do (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.....	0.05
Group Allocation	Equal (N_{BT} = N_{BC})
Equivalence Limit Input Type.....	Enter the equivalence limit proportion f, where E = f × Do
f (Equivalence Proportion 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

Bridging Study using the Equivalence Test of Two Groups (Continuous Outcome)

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: $H_0: \theta \leq -E \text{ or } \theta \geq E$ vs. $H_1: -E < \theta < E$
 H1 Assumption: $\theta = 0$

Bridging Study										Original Study				
Power	Sample Size			Equivalence		Standard Deviation		Alpha	Sample Size		Mean Difference Do	Standard Deviation		
				Proportion of Do f	Limit Magnitude E	Treatment σBT	Control σBC					Treatment SoT	Control SoC	

0.80010	729	729	1458	0.2	2.266	11.86	10.39	0.05	973	948	11.33	11.86	10.39
0.80009	228	228	456	0.3	3.399	11.86	10.39	0.05	973	948	11.33	11.86	10.39
0.80321	117	117	234	0.4	4.532	11.86	10.39	0.05	973	948	11.33	11.86	10.39

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 NB_T The number of bridging study subjects assigned to the treatment group.
 NB_C The number of bridging study subjects assigned to the control group.
 NB The total sample size of the bridging study.
 f The proportion of |Do| used as the magnitude of the equivalence limits. $E = f \times |Do|$.
 E The magnitude of the lower and upper equivalence limits: EL and EU. $EL = -|E|$ and $EU = |E|$.
 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.
 No_T The number of subjects assigned to the treatment group in the original study.
 No_C The number of subjects assigned to the control group in the original study.
 Do The difference between the group means ($\tau - c$) in the original study.
 So_T The response standard deviation of subjects assigned to the treatment group in the original study.
 So_C 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 ($\mu_{BT} - \mu_{BC}$) is equivalent to the original study mean difference ($\mu_{OT} - \mu_{OC}$), with a difference equivalence proportion of 0.2 corresponding to equivalence bounds of -2.266 and 2.266 ($H_0: \theta \leq -2.266 \text{ or } \theta \geq 2.266$ versus $H_1: -2.266 < \theta < 2.266$, where $\theta = (\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})$). The comparison will be made using two one-sided Z-tests based on the difference in treatment effects of the two regions, with an overall Type I error rate (α) of 0.05. 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 729 in the treatment group and 729 in the control group.

Bridging Study using the Equivalence Test of Two Groups (Continuous Outcome)

Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	N _{BT}	N _{BC}	N _B	N _{BT} '	N _{BC} '	N _B '	D _T	D _C	D
20%	729	729	1458	912	912	1824	183	183	366
20%	228	228	456	285	285	570	57	57	114
20%	117	117	234	147	147	294	30	30	60

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 _{BT} , N _{BC} , and N _B	The evaluable sample sizes at which power is computed (as entered by the user). If N _{BT} and N _{BC} subjects are evaluated out of the N _{BT} ' and N _{BC} ' subjects that are enrolled in the study, the design will achieve the stated power.
N _{BT} ', N _{BC} ', and N _B '	The number of subjects that should be enrolled in the study in order to obtain N _{BT} , N _{BC} , and N _B evaluable subjects, based on the assumed dropout rate. N _{BT} ' and N _{BC} ' are calculated by inflating N _{BT} and N _{BC} using the formulas $N_{BT}' = N_{BT} / (1 - DR)$ and $N_{BC}' = N_{BC} / (1 - DR)$, with N _{BT} ' and N _{BC} ' 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 _T , D _C , and D	The expected number of dropouts. $D_T = N_{BT}' - N_{BT}$, $D_C = N_{BC}' - N_{BC}$, and $D = D_T + D_C$.

Dropout Summary Statements

Anticipating a 20% dropout rate, 912 subjects should be enrolled in Group 1, and 912 in Group 2, to obtain final group sample sizes of 729 and 729, respectively.

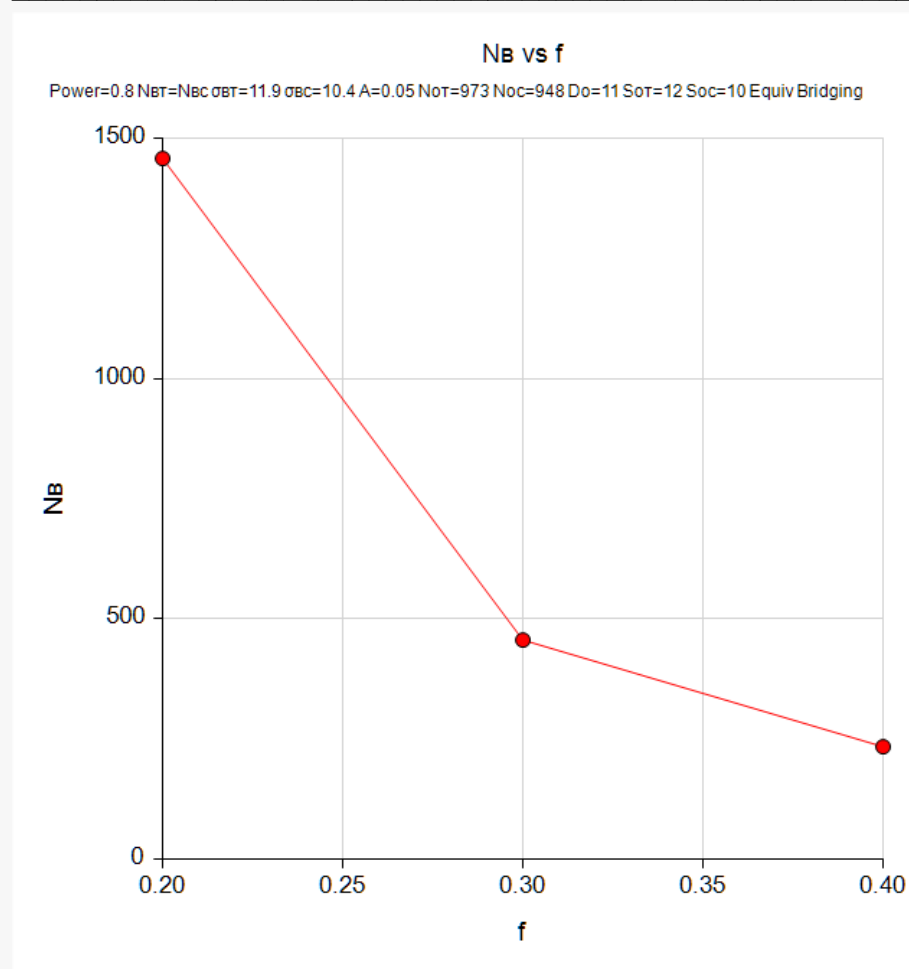
References

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 a table of example results on page 976. 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 80 per group (160 total).

These input values are consistent with the following summary statistics:

$$N_{OT} = 500 \quad \hat{\mu}_{OT} = 4 \quad s_{OT} = 0.8$$

$$N_{OC} = 500 \quad \hat{\mu}_{OC} = 2 \quad s_{OC} = 0.8$$

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
Do (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})
Equivalence Limit Input Type.....	Enter the equivalence limit proportion f, where E = f × Do
f (Equivalence Proportion of Do).....	0.2
σ _{BT} (Std Deviation of Group BT)	0.8
σ _{BC} (Std Deviation of Group BC).....	0.8

Bridging Study using the Equivalence Test of Two Groups (Continuous Outcome)

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: $H_0: \theta \leq -E \text{ or } \theta \geq E$ vs. $H_1: -E < \theta < E$

H1 Assumption: $\theta = 0$

Bridging Study									Original Study				
Power	Sample Size			Equivalence		Standard Deviation		Alpha	Sample Size		Mean Difference Do	Standard Deviation	
				Proportion of Do f	Limit Magnitude E	Treatment σBT	Control σBC					Treatment SoT	Control SoC
	NBT	NBC	NB										
	0.80338	80	80	160	0.2	0.4	0.8		0.8	0.05		500	500

PASS has also calculated a sample size of 80 per group, so the procedure is validated.