Chapter 263

Bridging Study using a Non-Inferiority Test of Two Groups (Binary 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. The response data is binary. 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 proportions 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 margin.

Test Statistics

This section summarizes the results found in Liu, Hsueh, and Chen (2002), page 974 - 976. Note that in the following presentation, since the response is binary, the mean response is also the proportion of responses in which the outcome is positive.

Original Study

Let Y_{ijk} be the binary response (0 or 1) 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 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 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

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

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 binary 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 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 1.

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

$$H_0{:}\, \theta \leq -NIM \;\; \text{vs} \;\; H_1{:}\, \theta > -NIM$$

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 $\beta = 1 - \text{Power}$, 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.

Note that since the variance of a Bernoulli random variable is $p(1-p)$, all four variance terms may be estimated from the corresponding proportions. For example, $\sigma_{BT}^2 = P_{BT}(1 - P_{BT})$.

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. The primary endpoint was binary. These trials resulted in the following summary statistics:

$N_{OT} = 973 \qquad \hat{\mu}_{OT} = 0.732$

$N_{OC} = 948 \qquad \hat{\mu}_{OC} = 0.508$

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 $P_{BT} = P_{OT}$ and $P_{BC} = P_{OC}$. They want to calculate the necessary sample size when f is 0.3, 0.4, or 0.5. 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**
Nᴏᴛ (Sample Size of Group ᴏᴛ)	**973**
Nᴏᴄ (Sample Size of Group ᴏᴄ)	**948**
Pᴏᴛ (Group ᴏᴛ Proportion)	**0.732**
Pᴏᴄ (Group ᴏᴄ Proportion)	**0.508**
Power	**0.8**
Alpha	**0.025**
Group Allocation	**Equal (Nʙᴛ = Nʙᴄ)**
Non-Inferiority Margin Input	**Enter f, the proportion NIM is of |Pᴏᴛ-Pᴏᴄ|**
f (Proportion NIM is of |Pᴏᴛ-Pᴏᴄ|)	**0.3 0.4 0.5**
Pʙᴛ (Group ʙᴛ Proportion)	**0.732**
Pʙᴄ (Group ʙᴄ Proportion)	**0.508**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Definition: θ = (PBT - PBC) - (POT - POC)
Hypotheses: H0: θ ≤ -NIM vs. H1: θ > -NIM
H1 Assumption: θ = 0

				Bridging Study					Original Study				
				Non-Inferiority		Proportions					Proportions		
Power	NBT	NBC	NB	Prop f	Value NIM	Trt PBT	Ctrl PBC	Alpha	NOT	NOC	Diff DO	Trt POT	Ctrl POC
0.80001	4053	4053	8106	0.3	0.0672	0.732	0.508	0.025	973	948	0.224	0.732	0.508
0.80024	801	801	1602	0.4	0.0896	0.732	0.508	0.025	973	948	0.224	0.732	0.508
0.80016	394	394	788	0.5	0.1120	0.732	0.508	0.025	973	948	0.224	0.732	0.508

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
NBT The number of bridging study subjects assigned to the treatment group.
NBC The number of bridging study subjects assigned to the control group.
NB The total sample size of the bridging study.
f The proportion of |POT - POC| used as the magnitude of the non-inferiority margin. NIM = f × |POT - POC|.
NIM The non-inferiority margin. L = -NIM or U = NIM. NIM > 0
PBT The response proportion of subjects assigned to the treatment group in the bridging study.
PBC The response proportion of subjects assigned to the control group in the bridging study.
Alpha The probability of rejecting a true null hypothesis.
NOT The number of subjects assigned to the treatment group in the original study.
NOC The number of subjects assigned to the control group in the original study.
DO The difference between the group proportions (T - C) in the original study.
POT The response proportion of subjects assigned to the treatment group in the original study.
POC The response proportion of subjects assigned to the control group in the original study.

Summary Statements

The bridging study sample sizes of 4053 in the treatment group and 4053 in the control group achieve 80% power using a non-inferiority test of the difference between the two group proportions. The significance level (alpha) of the equivalence test is 0.025. The non-inferiority margin is 0.0672. The bridging-study treatment-group proportion is 0.732. The bridging-study control-group proportion is 0.508. The summary statistics of the original study are as follows. The treatment group sample size was 973. The control group sample size was 948. The difference between the group proportions was 0.224. The treatment group proportion was 0.732. The control group proportion was 0.508.

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%	4053	4053	8106	5067	5067	10134	1014	1014	2028
20%	801	801	1602	1002	1002	2004	201	201	402
20%	394	394	788	493	493	986	99	99	198

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, 5067 subjects should be enrolled in Group 1, and 5067 in Group 2, to obtain final group sample sizes of 4053 and 4053, respectively.

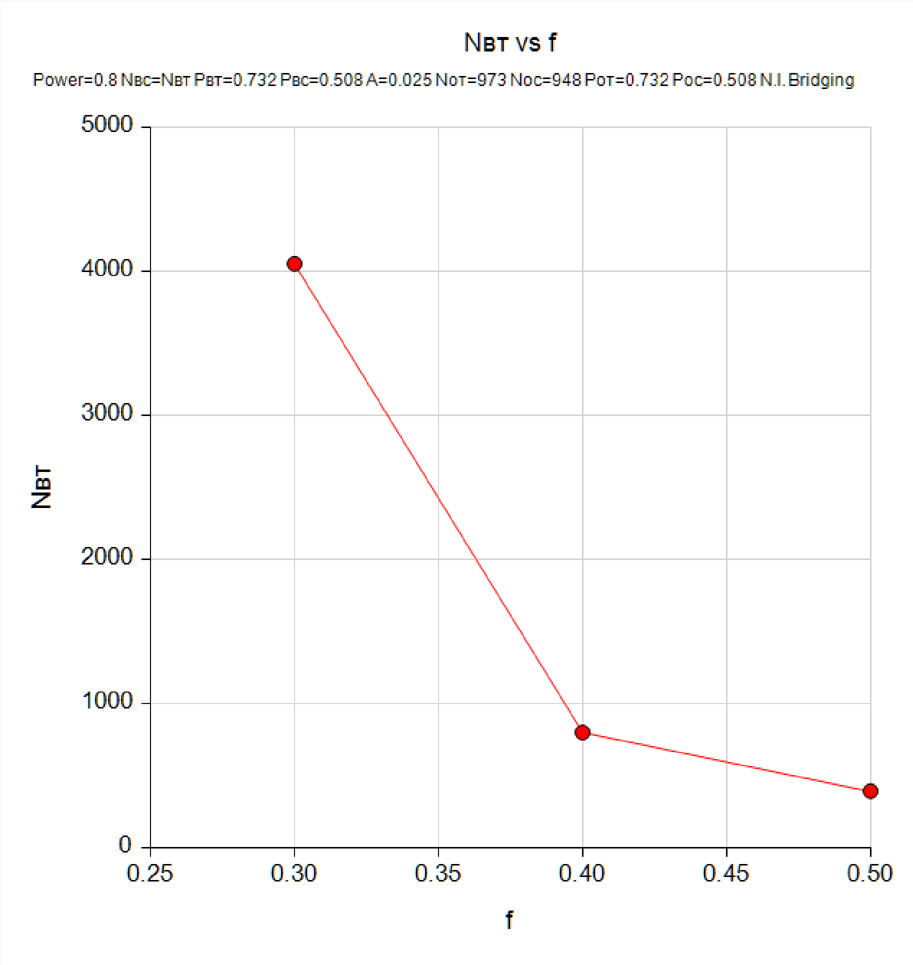
References

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 f 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 a Previously Validated Procedure

We could not find a validation example in the literature, so we will validate this procedure using the *Bridging Study using a Non-Inferiority Test of Two Groups* (*Continuous Outcomes*) procedure that has been validated.

The following example will be used for the validation. The summary statistics of the original study are

$$N_{OT} = 1000 \qquad P_{OT} = 0.8$$

$$N_{OC} = 1000 \qquad P_{OC} = 0.5$$

Note that $D_0 = 0.8 - 0.5 = 0.3$, $s_{OT} = \sqrt{0.8(0.2)} = 0.4$ and $s_{OC} = \sqrt{0.5(0.5)} = 0.5$. In the bridging study, set *f* = 0.4, *alpha* = 0.025, and *power* = 0.8.

These values translate to the following in the Continuous Outcomes procedure.

$$N_{OT} = 1000 \qquad D_O = 0.3 \qquad s_{OT} = 0.4$$

$$N_{OC} = 1000 \qquad \qquad s_{OC} = 0.5$$

Running these values through that procedure results in the following sample sizes for the bridging study: $N_{BT} = N_{BC} = 288$.

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**
NOT (Sample Size of Group OT)	**1000**
NOC (Sample Size of Group OC)	**1000**
POT (Group OT Proportion)	**0.8**
POC (Group OC Proportion)	**0.5**
Power	**0.8**
Alpha	**0.025**
Group Allocation	**Equal (NBT = NBC)**
Non-Inferiority Margin Input	**Enter f, the proportion NIM is of |POT-POC|**
f (Proportion NIM is of |POT-POC|)	**0.4**
PBT (Group BT Proportion)	**0.8**
PBC (Group BC Proportion)	**0.5**

Output

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

Numeric Results

Solve For: Sample Size
Definition: θ = (P_{BT} - P_{BC}) - (P_{OT} - P_{OC})
Hypotheses: H0: θ ≤ -NIM vs. H1: θ > -NIM
H1 Assumption: θ = 0

Bridging Study									Original Study				
				Non-Inferiority		Proportions					Proportions		
Power	N_{BT}	N_{BC}	N_B	Prop f	Value NIM	Trt P_{BT}	Ctrl P_{BC}	Alpha	N_{OT}	N_{OC}	Diff D_O	Trt P_{OT}	Ctrl P_{OC}
0.80022	288	288	576	0.4	0.12	0.8	0.5	0.025	1000	1000	0.3	0.8	0.5

This procedure has also calculated a sample size of 288 per group, so the procedure is validated.