Chapter 266

# Bridging Study Test of Sensitivity using a Two-Group T-Test (Continuous Outcome)

## Introduction

This procedure calculates the power and sample size required for bridging studies that two-sample, equal-variance t-test to estimate the sensitivity of the anticipated bridging study. The response data is continuous (assumed normal). Only a brief introduction to the subject will be given here. For a comprehensive discussion, refer to Chow, Shao, and Hu (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. After a value of the sensitivity index is obtained, an assessment must be made to determine whether the bridging study is necessary. If the bridging study is required, further analysis must be made to determine how large of a sample size is needed. This procedure helps with both of these questions.

### Sensitivity Index

Suppose a randomized, parallel-group, placebo-controlled study has been completed and used to evaluate a test compound for use in treating a certain disease in a particular population. Now suppose that the sponsors of the test compound want to obtain approval for use in another population. This new population may be a demographic (e.g., elderly) that was not represented in the original study, or it may be an additional world region (e.g., Japan). It is assumed that the response to the test compound will be similar but slightly different in the new region. The similarities between the response distributions in the two regions can be summarized by their means and variances.

As is described below, Chow, Shao, and Hu (2002) proposed that these population differences could be summarized as a single number called the *sensitivity index*. They proposed that this index be used when there are well known ethnic differences between the two populations. Rather than have two parameters (means and standard deviations) to use for evaluating the population differences, they proposed that the ratio of each region's signal-to-noise ratios could be used.

# Test Procedure for Assessing Sensitivity

Suppose a clinical trial using a typical parallel-group design has been completed and the treatment has been found to be beneficial in treating a certain disease. The analysis of this study, which is called the *original study*, is summarized as follows.

Let $X_{ij}$ be the response of subject *j* on receiving treatment *i* in original study where *i* = T (treatment), C (control) and $j = 1, \ldots, N_i$. Let $N = N_T + N_C$. Assume that the $X_{ij}$ are independently normally distributed with means $\mu_i$ and common variance $\sigma^2$. Suppose the statistical hypotheses to be tested are

$$H_0: \mu_T - \mu_C = 0 \quad vs. \quad H_1: \mu_T - \mu_C \neq 0$$

Assuming that the standard two-sample t-test is used for the analysis. The test statistic

$$T = \frac{\bar{x}_T - \bar{x}_C}{\sqrt{\left(\frac{(N_T - 1)S_T^2 + (N_C - 1)S_C^2}{N - 2}\right)\left(\frac{1}{N_T} + \frac{1}{N_C}\right)}}$$

is assumed to be distributed as a *Student's t* random variable with the usual degrees of freedom. The power of *T* is

$$p(\theta) = 1 - T'_{N-2}\left(t_{N-2,1-\frac{\alpha}{2}}\middle|\theta\right) + T'_{N-2}\left(-t_{N-2,1-\frac{\alpha}{2}}\middle|\theta\right)$$

where $t_{N-2,1-\frac{\alpha}{2}}$ is t-value from the central *t* distribution, $T'_{N-2}$ is the distribution function of the noncentral *t* distribution, and $\theta$ is the noncentrality parameter calculated as

$$\theta = \frac{\mu_T - \mu_C}{\sigma\sqrt{\left(\frac{1}{N_T} + \frac{1}{N_C}\right)}}$$

Suppose *x* represents the data from the original trial and $T(x)$ is the value of *T* based on *x.* If $\theta$ is replaced by $T(x)$ in the power function above, the *estimated power* $\hat{P}\big(T(x)\big) = p\big(T(x)\big)$ is defined by Shao and Chow (2002) as the *reproducibility probability* for the bridging trial with the same subject population and with the same sample size.

Define $T^*$ to be the value of *T* obtained when $N_T$ and $N_C$ of the original study is replaced by $N_T^*$ and $\mathrm{N_C^*}$ which are the corresponding sample sizes of the bridging study. The estimated power of the new study is given by $\hat{P}\big(T^*(x)\big)$.

Suppose the mean responses in the treatment and control groups of the original study are named $\mu_{OT}$ and $\mu_{OC}$. Further suppose a single variance, $\sigma_O^2$, can be used for both groups of the original study. Similar quantities in the new region are $\mu_{BT}, \mu_{BC}$, and $\sigma_B^2$.

Let the relative difference between means in the two regions be defined as

$$R_{MD} = \frac{(\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})}{(\mu_{OT} - \mu_{OC})}$$

Similarly, let the ratio between standard deviations in the two regions be defined as

$$R_{SD} = \frac{\sigma_B}{\sigma_O}$$

The signal-to-noise ratio of the difference in the bridging study is $(\mu_{OT} - \mu_{OC})/\sigma_O$. Similarly, the signal-to-noise ratio of the difference in the bridging study is $(\mu_{BT} - \mu_{BC})/\sigma_B$.

The ratio of the two-study region signal-to-noise ratios of the differences between these parameters is

$$\Delta = \frac{(\mu_{BT} - \mu_{BC})/\sigma_B}{(\mu_{OT} - \mu_{OC})/\sigma_O}$$

which is called the *sensitivity index.* A little algebra will show that this can be rewritten as

$$\Delta = \frac{1 + R_{MD}}{R_{SD}}$$

Hence Δ is a measure of the change in signal-to-noise ratio from the original study to the bridging study.

Note that Δ may be computed for different values of $R_{MD}$ and $R_{SD}$ using the *Bridging Study Sensitivity Index* procedure in PASS.

## Power and Sample Size of the Bridging Study

Chow, Shao, and Hu (2002) define $\hat{P}(\Delta T(x))$ as the probability of generalizability of the results of the original population to the new population.

If it is determined that a bridging study must be conducted, $\hat{P}(\Delta T^*(x))$ estimates the power of that study at a given sample size. Using a simple search algorithm, this power estimate can be used to determine an appropriate sample size for the bridging study.

# Example 1 – Finding Sample Size

Chow, Shao, and Hu (2002) page 394 present the following example. A certain drug has been cleared for use in the originally studied region using a two-sample t-test from a design with both a treatment group and a control group. The trial resulted in the following summary statistics:

$N_{OT} = 30$ $\bar{x}_{OT} = 19.8$ $s_{OT} = 8.4$

$N_{OC} = 30$ $\bar{x}_{OC} = 26.5$ $s_{OC} = 9.3$

Sponsors in another region not included in the original study would like to register this drug for use in that region as well. They want to assess the generalizability if the sensitivity index, Δ, is between 0.7 and 0.9. They also want to determine the reduction probability of the original study, so they add $\Delta = 1.0$ to the list.

In this new region, the policy is that a bridging study is not necessary if there is no more than a 10% reduction in the reproducibility probability of the original study.

If a bridging study is found necessary, they would like to determine sample necessary to obtain a power of 0.7 with a significance level of 0.05. 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) | **30** |
| Noc (Sample Size of Group oc) | **30** |
| Do (Mean Difference) | **-6.7** |
| Sᴏᴛ (Std Deviation of Group ᴏᴛ) | **8.4** |
| Soc (Std Deviation of Group oc) | **9.3** |
| Power of Bridging Study | **0.7** |
| Alpha | **0.05** |
| Group Allocation | **Equal (Nʙᴛ = Nʙc)** |
| Δ (Sensitivity Index) | **0.7 0.75 0.8 0.85 0.9 1** |

# Output

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

## Numeric Reports

**Numeric Results**

Solve For: Sample Size
Hypotheses: H0: $\mu_{BT} - \mu_{BC} = 0$ vs. H1: $\mu_{BT} - \mu_{BC} \neq 0$

| Bridging Study | | | | | | Original Study | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Power** | **$N_{BT}$** | **$N_{BC}$** | **$N_B$** | **Δ** | **Alpha** | **Power'** | **$N_{OT}$** | **Noc** | **Diff** | **$S_{OT}$** | **Soc** |
| 0.70923 | 46 | 46 | 92 | 0.70 | 0.05 | 0.52230 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70702 | 40 | 40 | 80 | 0.75 | 0.05 | 0.57920 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70351 | 35 | 35 | 70 | 0.80 | 0.05 | 0.63450 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70180 | 31 | 31 | 62 | 0.85 | 0.05 | 0.68713 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70563 | 28 | 28 | 56 | 0.90 | 0.05 | 0.73620 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70807 | 23 | 23 | 46 | 1.00 | 0.05 | 0.82109 | 30 | 30 | -6.7 | 8.4 | 9.3 |

| | |
|---|---|
| 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. |
| Δ | The sensitivity index. This is the ratio of the signal-to-noise ratios in the bridging study and the original study. |
| Alpha | The probability of rejecting a true null hypothesis. |
| Power' | The power of the test in the original study assuming that the parameter values are the sample values and that the noncentrality parameter is Δ × T. This value is used to determine whether the bridging study is necessary. |
| $N_{OT}$ | 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. |
| Diff | 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. |
| Soc | The response standard deviation of subjects assigned to the control group in the original study. |

**Summary Statements**

The bridging study sample sizes of 46 in the treatment group and 46 in the control group achieve 71% power using an equal-variance, two-sided t-test of the difference between the two group means. The significance level (alpha) of the test is 0.05. The ratio of the bridging study and original study signal-to-noise ratios is 0.7. The summary statistics of the original study are as follows. The treatment group sample size was 30. The control group sample size was 30. The difference between the group means was -6.7. The treatment group standard deviation was 8.4. The control group standard deviation was 9.3.

**Dropout-Inflated Sample Size**

| | Sample Size | | | Dropout-Inflated Enrollment Sample Size | | | Expected Number of Dropouts | | |
|---|---|---|---|---|---|---|---|---|---|
| Dropout Rate | $N_{BT}$ | $N_{BC}$ | $N_B$ | $N_{BT}'$ | $N_{BC}'$ | $N_B'$ | $D_T$ | $D_C$ | $D$ |
| 20% | 46 | 46 | 92 | 58 | 58 | 116 | 12 | 12 | 24 |
| 20% | 40 | 40 | 80 | 50 | 50 | 100 | 10 | 10 | 20 |
| 20% | 35 | 35 | 70 | 44 | 44 | 88 | 9 | 9 | 18 |
| 20% | 31 | 31 | 62 | 39 | 39 | 78 | 8 | 8 | 16 |
| 20% | 28 | 28 | 56 | 35 | 35 | 70 | 7 | 7 | 14 |
| 20% | 23 | 23 | 46 | 29 | 29 | 58 | 6 | 6 | 12 |

| | |
|---|---|
| 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, 58 subjects should be enrolled in Group 1, and 58 in Group 2, to obtain final group sample sizes of 46 and 46, respectively.

**References**

Shao, J. and Chow, S.C. 2002. 'Reproducibility probability in clinical trials.' Statistics in Medicine, Volume 21, Pages 1727-1742.

Chow, S.C., Shao, J. and Hu, O.Y.P. 2002. 'Assessing sensitivity and similarity in bridging studies.' Journal of Biopharmaceutical Statistics. Volume 12(3), Pages 385-400.

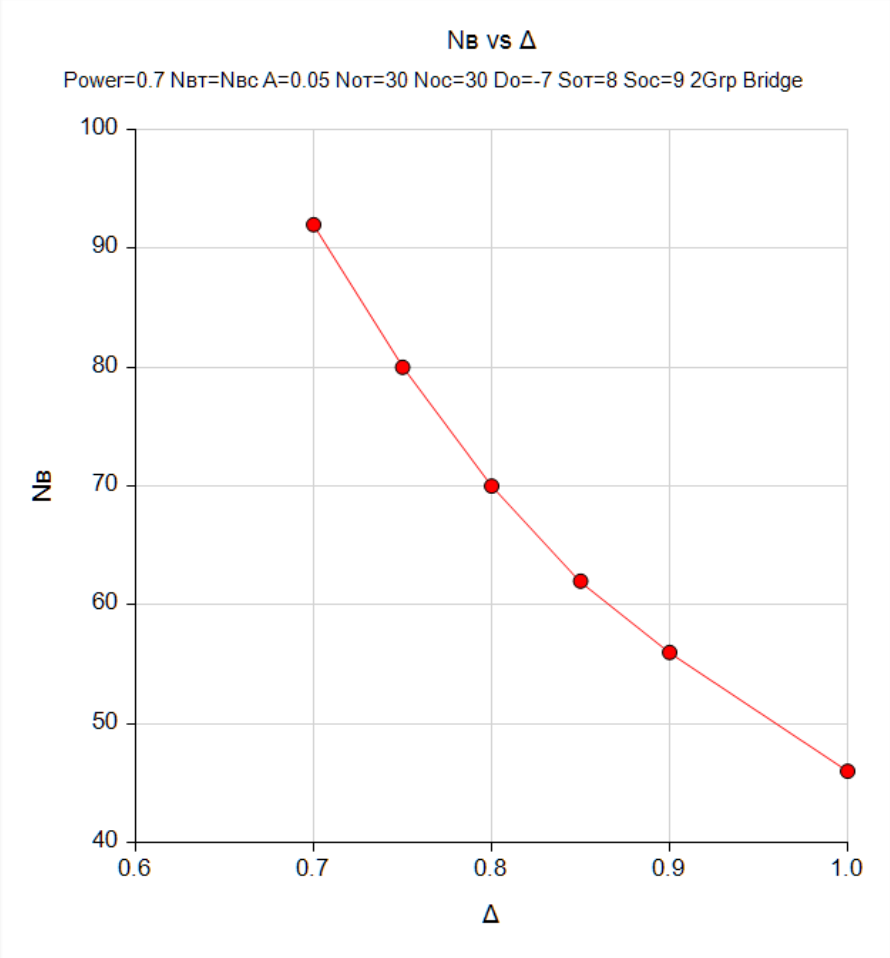
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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

The first question to be answered is whether a bridging study is necessary. The last row of the report shows the reproducibility probability (Power') to be 0.82109. The policy in the new region is that Power' be no less than 10% below this value. This results in a cutoff of $0.82109 \times 0.9 = 0.73898$. The Power' for $\Delta = 0.9$ is 0.73620 which is still below the cutoff of 0.73898. Hence, for any of the sensitivity index values between 0.7 and 0.9, the decision would be to run the bridging study. The $N_B$ column gives the required sample size to achieve 70% power. For example, if the anticipated value of $\Delta = 0.8$, a sample size of 35 per group is required.

## Plots Section

**Plots**




This plot shows the sample size versus sensitivity index.

# Example 2 – Validation using Chow, Shao, and Hu (2002)

Chow, Shao, and Hu (2002) page 394 present the following example which we will use to validate this procedure. A certain drug has been cleared for use in the originally studied region using a two-sample t-test from a design with both a treatment group and a control group. The trial resulted in the following summary statistics as shown in Table 4:

$N_{OT} = 30$ $\bar{x}_{OT} = 19.8$ $s_{OT} = 8.4$

$N_{OC} = 30$ $\bar{x}_{OC} = 26.5$ $s_{OC} = 9.3$

Sponsors in another region not included in the original study would like to register this drug for use in that region as well. They want to assess the generalizability if the sensitivity index, Δ, is between 0.7 and 0.85.

In Table 5 on page 394 obtained the following sample sizes for Δ between 0.7 and 0.85: 92, 80, 70, and 62.

## 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** |
| Nот (Sample Size of Group от) | **30** |
| Noc (Sample Size of Group oc) | **30** |
| Do (Mean Difference) | **-6.7** |
| Sот (Std Deviation of Group от) | **8.4** |
| Soc (Std Deviation of Group oc) | **9.3** |
| Power of Bridging Study | **0.7** |
| Alpha | **0.05** |
| Group Allocation | **Equal (Nвт = Nвс)** |
| Δ (Sensitivity Index) | **0.7 0.75 0.8 0.85** |

# Output

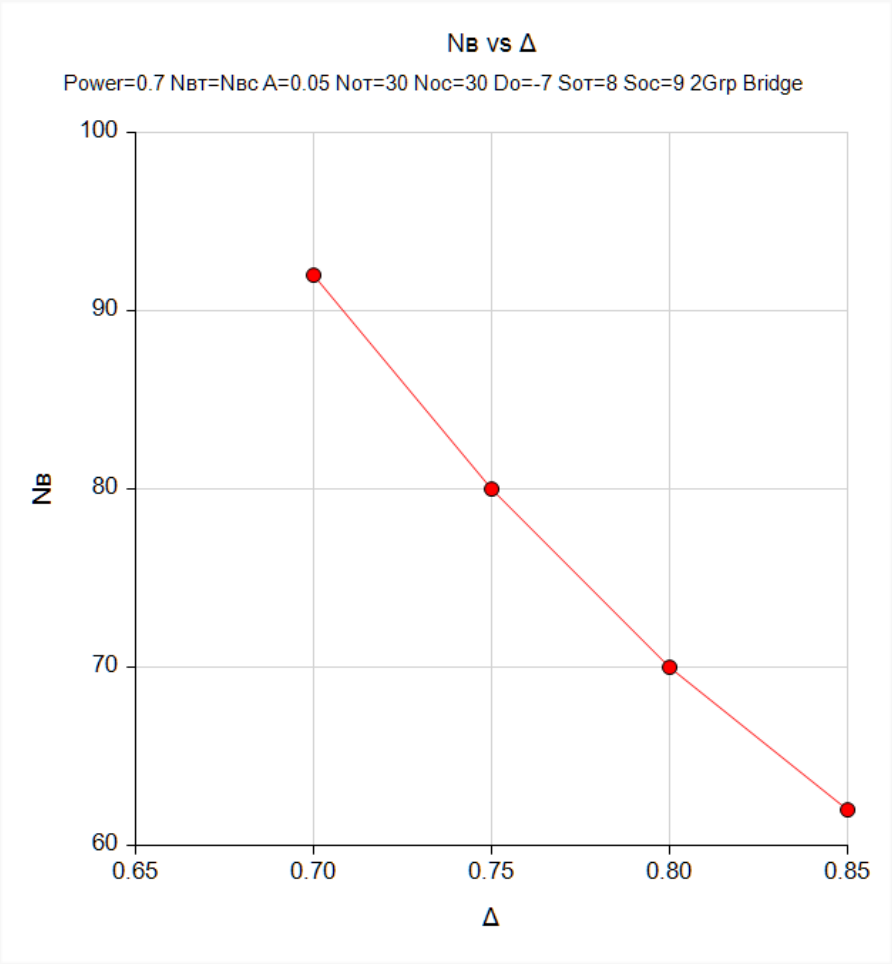
Click the Calculate button to perform the calculations and generate the following output.

**Numeric Results**

Solve For: Sample Size
Hypotheses: H0: μBT - μBC = 0 vs. H1: μBT - μBC ≠ 0

| Bridging Study | | | | | | Original Study | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Power | NBT | NBC | NB | Δ | Alpha | Power' | NOT | NOC | Diff | SOT | SOC |
| 0.70923 | 46 | 46 | 92 | 0.70 | 0.05 | 0.52230 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70702 | 40 | 40 | 80 | 0.75 | 0.05 | 0.57920 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70351 | 35 | 35 | 70 | 0.80 | 0.05 | 0.63450 | 30 | 30 | -6.7 | 8.4 | 9.3 |
| 0.70180 | 31 | 31 | 62 | 0.85 | 0.05 | 0.68713 | 30 | 30 | -6.7 | 8.4 | 9.3 |

**Plots**




**PASS** has also calculated sample sizes of 92, 80, 70, and 62 so the procedure is validated. The plot shows the sample size versus sensitivity index.