

Chapter 264

Bridging Study Sensitivity Index

Introduction

This procedure calculates the *sensitivity index* for a bridging study that will compare two study regions: original and bridging. 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. 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.

In some cases, a bridging study is not necessary. The sensitivity index helps with this go/no go decision.

Sensitivity Index

This section summarizes the results found in Chow, Shao, and Hu (2002) and in Chow *et al.* (2018) page 449.

Original Study

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 get it approved 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 in the two regions can be summarized by means and variances.

Chow, Shao, and Hu (2002) proposed that these population differences could be summarized as a single number which they named the sensitivity index. Specifically, 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.

Suppose that the mean responses in the treatment and control groups of the original study are μ_{OT} and μ_{OC} . Further suppose that a single variance, σ_O^2 , can be used for both groups of the original study. Similar quantities in the new region are μ_{BT} , μ_{BC} , and σ_B^2 .

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The ratio of the two-study region signal-to-noise ratios are

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

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 sensitivity index can then be rewritten as

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

This sensitivity index can be used by another **PASS** procedure to estimate the so-called *reproducibility probability*.

Example 1 – Calculating the Sensitivity Index

Calculate the sensitivity index for $R_{MD} = 0.05, 0.10, 0.15, 0.20$ and $R_{SD} = 0.8, 1.0, 1.25$.

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

RMD (Ratio of Mean Differences) **0.05 0.1 0.15 0.2**

RSD (Ratio of Standard Deviations) **0.8 1.0 1.25**

Output

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

Numeric Reports

Numeric Results

Solve For: **Sensitivity Index (Δ)**

Ratio of Study Regions

Sensitivity Index Δ	Mean Differences RMD	Standard Deviations RSD
1.3125	0.05	0.80
1.0500	0.05	1.00
0.8400	0.05	1.25
1.3750	0.10	0.80
1.1000	0.10	1.00
0.8800	0.10	1.25
1.4375	0.15	0.80
1.1500	0.15	1.00
0.9200	0.15	1.25
1.5000	0.20	0.80
1.2000	0.20	1.00
0.9600	0.20	1.25

Δ The sensitivity index is the ratio of the study region signal-to-noise-ratios. $\Delta = \text{SNR}(\text{Bridging}) / \text{SNR}(\text{Original})$.

RMD The ratio of the study region mean differences. $\text{RMD} = ((\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})) / (\mu_{OT} - \mu_{OC})$.

RSD The ratio of the study region standard deviations. $\text{RSD} = \sigma_B / \sigma_O$.

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Summary Statements

The sensitivity index (ratio of the bridging study region signal-to-noise ratio to the original region signal-to-noise ratio) gives an assessment of the effect size shift between the two regions. If the relative difference of the study region mean differences, $[(\mu_{BT} - \mu_{BC}) - (\mu_{OT} - \mu_{OC})] / (\mu_{OT} - \mu_{OC})$, is 0.05, and the ratio of the study region standard deviations, σ_B / σ_O , is 0.8, the sensitivity index (the change in the signal-to-noise ratio for the population difference) is 1.3125.

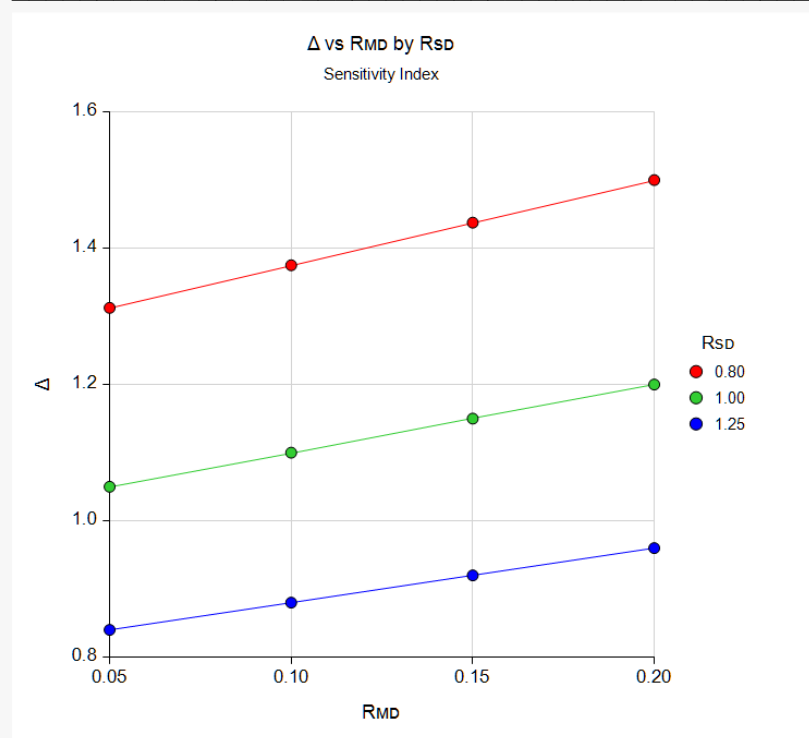
References

Chow, S.C., Shao, J., and Hu, O.Y.P. 2002. 'Assessing Sensitivity and Similarity in Bridging Studies.' Journal of Biopharmaceutical Statistics, Vol 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.

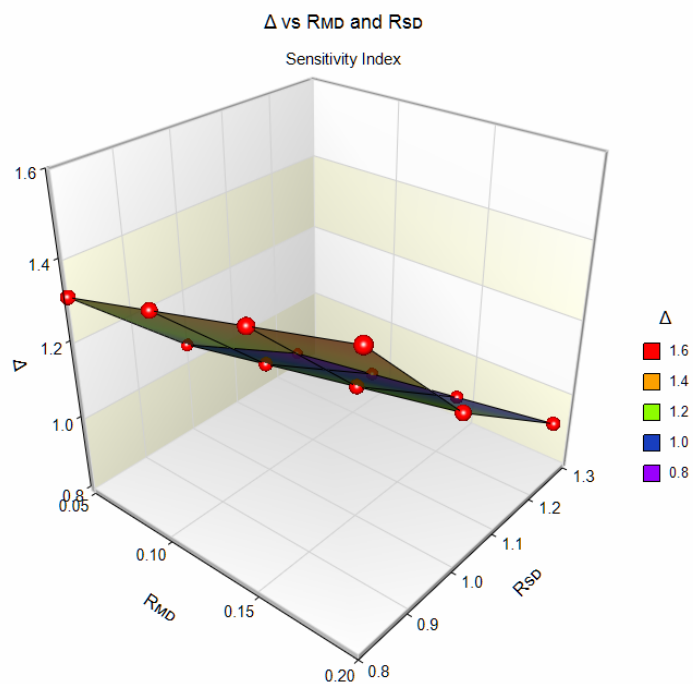
This report shows the sample size for the indicated parameter configurations.

Plots Section

Plots



Bridging Study Sensitivity Index



These plots show the sensitivity index for various combinations of R_{MD} and R_{SD} .

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

Chow *et al.* (2002) include Table 1 of sample results on page 389. Set $R_{MD} = 0.05$ and $R_{SD} = 0.8$. The resulting value is $\Delta = 1.313$.

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

RMD (Ratio of Mean Differences) **0.05**

RSD (Ratio of Standard Deviations) **0.8**

Output

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

Numeric Results

Solve For: [Sensitivity Index \(\$\Delta\$ \)](#)

Ratio of Study Regions

Sensitivity Index Δ	Mean Differences RMD	Standard Deviations RSD
1.3125	0.05	0.8

PASS has calculated $\Delta = 1.3125$, so the procedure is validated.