

Chapter 545

Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design

Introduction

This procedure calculates power and sample size of statistical tests of equivalence of two means of higher-order cross-over designs when the analysis uses a t-test or equivalent. The parameter of interest is the ratio of the two means. Schuirmann's (1987) two one-sided tests (TOST) approach is used to test equivalence. Only a brief introduction to the subject will be given here. For a comprehensive discussion on the subject, refer to Chen, Chow, and Li (1997). The designs covered in this chapter are analyzed using what is called the 'multiplicative model' in Chen et al (1997). The 'additive model' is covered in the procedure that uses differences. Note that the multiplicative model is simply an additive model applied to the logarithmic transform of the original data.

Measurements are made on individuals that have been randomly assigned to one of several treatment sequences. This *cross-over* design may be analyzed by a TOST equivalence test to show that the two means do not differ by more than a small amount, called the margin of equivalence.

Cross-Over Designs

Senn (2002) defines a *cross-over* design as one in which each subject receives all treatments at least once and the object is to study differences among the treatments. The name *cross-over* comes from the most common case in which there are only two treatments. In this case, each subject *crosses over* from one treatment to another. It is assumed that there is a *washout* period between treatments during which the response returns to its baseline value. If this does not occur, there is said to be a *carryover* effect.

A 2x2 cross-over design refers to two treatments (periods) and two *sequences* (treatment orderings). One sequence of treatments is treatment A followed by treatment B. The other sequence is B and then A. The design includes a washout period between responses to make certain that the effects of the first drug do no carryover to the second. Thus, the groups of subjects in this design are defined by the sequence in which the two treatments are administered, not by the treatments they receive.

Higher-Order Cross-Over Designs

Chen et al. (1997) present the results for four cross-over designs that are more complicated than the 2x2 design. Assume that the two treatments are labeled A and B. The available designs are defined by the order and number of times the two treatments are administered.

Balaam's Design

Balaam's design has four sequences with two treatments each. It is popular because it allows the intrasubject variabilities to be estimated. The design is

<u>Sequence</u>	<u>Period 1</u>	<u>Period 2</u>
1	A	A
2	B	B
3	A	B
4	B	A

Two-Sequence Dual Design

This design has two sequences with three periods each. It is popular because it allows the intrasubject variabilities to be estimated. The design is

<u>Sequence</u>	<u>Period 1</u>	<u>Period 2</u>	<u>Period 3</u>
1	A	B	B
2	B	A	A

Four-Period Design with Two Sequences

This design has two sequences of four periods each. The design is

<u>Sequence</u>	<u>Period 1</u>	<u>Period 2</u>	<u>Period 3</u>	<u>Period 4</u>
1	A	B	B	A
2	B	A	A	B

Four-Period Design with Four Sequences

This design has four sequences of four periods each. The design is

<u>Sequence</u>	<u>Period 1</u>	<u>Period 2</u>	<u>Period 3</u>	<u>Period 4</u>
1	A	A	B	B
2	B	B	A	A
1	A	B	B	A
2	B	A	A	B

Advantages of Cross-Over Designs

A comparison of treatments on the same subject is expected to be more precise. The increased precision often translates into a smaller sample size. Also, patient enrollment may be easier to obtain because each patient will receive both treatments.

Disadvantages of Cross-Over Designs

The statistical analysis of a cross-over experiment is more complex than a parallel-group experiment and requires additional assumptions. In a cross-over experiment, it may be difficult to separate the treatment effect from the time effect and the carry-over effect of the previous treatment.

These cross-over designs cannot be used when the treatment (or the measurement of the response) alters the subject permanently. Hence, it cannot be used to compare treatments that are intended to provide a cure.

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Because subjects must be measured at least twice, it may be more difficult to keep patients enrolled in the study. This is particularly true when the measurement process is painful, uncomfortable, embarrassing, or time consuming.

Outline of an Equivalence Test

PASS follows the *two one-sided tests* approach described by Schuirmann (1987) and Phillips (1990). It will be convenient to adopt the following specialized notation for the discussion of these tests.

<u>Parameter</u>	<u>PASS Input/Output</u>	<u>Interpretation</u>
μ_T	Not used	<i>Treatment mean.</i> This is the treatment mean.
μ_R	Not used	<i>Reference mean.</i> This is the mean of a reference population.
ϕ_L, ϕ_U	RL, RU	<i>Margin of equivalence.</i> These limits define an interval of the ratio of the means in which their difference is so small that it may be ignored.
ϕ	R1	<i>True ratio.</i> This is the value of $\phi = \mu_T / \mu_R$ at which the power is calculated.

Note that the actual values of μ_T and μ_R are not needed. Only their ratio is needed for power and sample size calculations.

The null hypothesis of non-equivalence is

$$H_0: \phi \leq \phi_L \text{ or } \phi \geq \phi_U \text{ where } \phi_L < 1, \phi_U > 1.$$

The alternative hypothesis of equivalence is

$$H_1: \phi_L < \phi < \phi_U$$

Log-Transformation

In many cases, hypotheses stated in terms of ratios are more convenient than hypotheses stated in terms of differences. This is because ratios can be interpreted as percentages, but differences must be interpreted as actual amounts in their original scale. Also, the distributions of variables such as CMax or AUC are often skewed. Hence, a common practice is to take the following steps in hypothesis testing.

1. State the statistical hypothesis in terms of a ratio.
2. Transform this into a hypothesis about the difference by taking logarithms.
3. Analyze the logged data—that is, do the analysis in terms of the difference.
4. Draw the conclusion in the original ratio scale.

The details of step 2 for the alternative hypothesis are as follows.

$$\begin{aligned} \phi_L &< \phi < \phi_U \\ \Rightarrow \phi_L &< \left\{ \frac{\mu_T}{\mu_R} \right\} < \phi_U \\ \Rightarrow \ln(\phi_L) &< \left\{ \ln(\mu_T) - \ln(\mu_R) \right\} < \ln(\phi_U) \end{aligned}$$

Thus, a hypothesis about the ratio of the means on the original scale can be translated into a hypothesis about the difference of two means on the logged scale.

Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design

When performing an equivalence test on the difference between means, the usual procedure is to set the equivalence limits symmetrically above and below zero. Thus, the equivalence limits will be plus or minus an appropriate amount. The common practice is to do the same when the data are being analyzed on the log scale. However, when symmetric limits are set on the log scale, they do not translate to symmetric limits on the original scale. Instead, they translate to limits that are the inverses of each other.

Perhaps these concepts can best be understood by considering an example. Suppose the researchers have determined that the lower equivalence limit should be 80% on the original scale. Since they are planning to use a log scale for their analysis, they transform this limit into the log scale by taking the logarithm of 0.80. The result is -0.223144. Wanting symmetric limits, they set the upper equivalence limit to 0.223144. Exponentiating this value, they find that $\exp(0.223144) = 1.25$. Note that $1/(0.80) = 1.25$. Thus, the limits on the original scale are 80% and 125%, not 80% and 120%.

Using this procedure, appropriate equivalence limits for the ratio of two means can be easily determined. Here are a few sets of equivalence limits for ratios.

Specified Percent Change	Lower Limit Original Scale	Upper Limit Original Scale	Lower Limit Log Scale	Upper Limit Log Scale
-25%	75.0%	133.3%	-0.287682	0.287682
+25%	80.0%	125.0%	-0.223144	0.223144
-20%	80.0%	125.0%	-0.223144	0.223144
+20%	83.3%	120.0%	-0.182322	0.182322
-10%	90.0%	111.1%	-0.105361	0.105361
+10%	90.9%	110.0%	-0.095310	0.095310

Note that negative percent-change values specify the lower limit first, while positive percent-change values specify the upper limit first. After the first limit is found, the other limit is calculated as its inverse.

Coefficient of Variation

The coefficient of variation (COV or CV) as it is used here is the ratio of the standard deviation to the reference mean. This parameter can be used to represent the variation in the data because of a unique relationship that it has in the case of log-normal data.

Suppose the variable X is the logarithm of the original variable Y . That is, $X = \ln(Y)$ and $Y = \exp(X)$. Label the mean and variance of X as μ_X and σ_X^2 , respectively. Similarly, label the mean and variance of Y as μ_Y and σ_Y^2 , respectively. If X is normally distributed, then Y is log-normally distributed. Julious (2004) presents the following well-known relationships between these two variables

$$\mu_Y = \left(e^{\mu_X + \frac{\sigma_X^2}{2}} \right)$$

$$\sigma_Y^2 = \mu_Y^2 \left(e^{\sigma_X^2} - 1 \right)$$

From this relationship, the coefficient of variation of Y can be expressed as

$$COV_Y = \frac{\sqrt{\mu_Y^2 \left(e^{\sigma_X^2} - 1 \right)}}{\mu_Y}$$

$$= \sqrt{e^{\sigma_X^2} - 1}$$

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Solving this relationship for σ_X^2 , the standard deviation of X can be stated in terms of the coefficient of variation of Y . This equation is

$$\sigma_X = \sqrt{\ln(COV_Y^2 + 1)}$$

Similarly, the mean of X is

$$\mu_X = \frac{\mu_Y}{\ln(COV_Y^2 + 1)}$$

Thus, the hypotheses can be stated in the original (Y) scale and then the power can be analyzed in the transformed (X) scale.

Test Statistics

The analysis for assessing equivalence using higher-order cross-over designs is discussed in detail in Chapter 9 of Chow and Liu (2000). Unfortunately, their presentation is too lengthy to give here. Their method involves the computation of an analysis of variance to estimate the error variance. It also describes the construction of confidence limits for appropriate contrasts. These confidence limits can then be compared to the equivalence limits to test for equivalence. We refer you to their book for details.

Power Calculation

The power is given by

$$Power(\phi) = T_V \left(\frac{\ln(\phi_U) - |\ln(\phi)|}{CV_m \sqrt{b/n}} - t_{V,1-\alpha} \right) - T_V \left(t_{V,1-\alpha} - \frac{|\ln(\phi)| - \ln(\phi_L)}{CV_m \sqrt{b/n}} \right)$$

where

$CV_m = \sqrt{\exp(MSE_{\log_{ged}}) - 1}$, T represents the cumulative t distribution, V and b depend on the design, and n is the average number of subjects per sequence. Note that the constants V and b depend on the design as follows.

<u>Design Type</u>	<u>Parameters (V, b)</u>
Balaam's Design	$V = 4n - 3, b = 2.$
Two-Sequence Dual Design	$V = 4n - 4, b = 3/4.$
Four-Period Design with Two Sequences	$V = 6n - 5, b = 11/20.$
Four-Period Design with Four Sequences	$V = 12n - 5, b = 1/4.$

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains the parameters associated with this test such as the means, sample sizes, alpha, and power.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. Under most situations, you will select either *Power* for a power analysis or *Sample Size* for sample size determination.

Select *Sample Size* when you want to calculate the sample size needed to achieve a given power and alpha level. Note that there are two choices for finding *Sample Size*. Select *Sample Size (Equal Per Sequence)* when you want the design to have an equal number of subjects per sequence. Select *Sample Size (Exact)* when you want to find the exact sample size even though the number of subjects cannot be dividing equally among the sequences.

Select *Power* when you want to calculate the power of an experiment.

Test

Design Type

Specify which cross-over design that you want to analyze. These designs allow you to compare two means: a treatment (A) and a reference (B). The designs assume that each subject is measured two or more times (or periods) with ample time in between to wash-out the effect of the treatment.

A sequence is an ordering of the how A and B are applied. For example, 'ABA' means that the subjects are measured three times: first treatment A, then B, then A again. Other possible sequences are BAB, AAB, and BBA. Each design includes several sequences.

The design tries to balance the experiment so that each treatment occurs an equal number of times and after each other treatment an equal number of times.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

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Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Total Sample Size)

This option specifies one or more values of the sample size, the number of individuals in the study (total subjects in all sequences). This value must be an integer greater than one.

You may enter a list of values using the syntax *50,100,150,200,250* or *50 to 250 by 50*.

Effect Size – Equivalence Limits

RU (Upper Equivalence Limit)

Enter the upper equivalence limit for the ratio of the two means. When the ratio of the means is between this value and RL, the two means are said to be equivalent. The value must be greater than one. A popular choice is 1.25.

Note that this value is not a percentage.

If you enter $1/RL$, then $1/RL$ will be calculated and used here. This choice is commonly used because RL and $1/RL$ give limits that are of equal magnitude on the log scale.

RL (Lower Equivalence Limit)

Enter the lower equivalence limit for the ratio of the two means. When the ratio of the means is between this value and RU, the two means are said to be equivalent. The value must be less than one. A popular choice is 0.80. Note that this value is not a percentage.

If you enter $1/RU$, then $1/RU$ will be calculated and used here. This choice is commonly used because RU and $1/RU$ give limits that are of equal magnitude on the log scale.

Effect Size – True Ratio

R1 (True Ratio)

This is the value of the ratio of the two means at which the power is to be calculated. Usually, the ratio will be assumed to be one. However, some authors recommend calculating the power using a ratio of 1.05 since this will require a larger, more conservative, sample size.

Effect Size – Coefficient of Variation

COV (Coefficient of Variation of Y)

A response variable Y has mean μ_Y and standard deviation σ_Y . The coefficient of variation of Y, σ_Y/μ_Y , is used to specify the variation in Y.

Suppose that Y is skewed, so a logarithmic transformation will be applied. That is, the variable $X = \ln(Y)$ will be analyzed using an appropriate ANOVA procedure. The analysis assumes that X is normally distributed with mean μ_X and standard deviation σ_X . So Y is lognormal and X is normal. Power and sample size calculations are made on X. However, interpretation may be easier in the Y scale.

Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design

If Y is truly lognormal, there is a direct relationship between μ_Y and σ_Y and μ_X and σ_X . Using this relationship, it can be shown that

$$COV_Y = \sqrt{\text{Exp}(\sigma_X^2) - 1}$$

Solving for σ_X , we obtain

$$\sigma_X = \sqrt{\ln(COV_Y^2 + 1)}$$

There are two ways to obtain a value for COV_Y .

1. Calculate COV_Y directly from the mean and SD of a set of Y values obtained from a previous (or pilot) study.
2. Obtain σ_{W_X} as the square root of the within mean square error in an ANOVA table of X. Then use the fact that $\sigma_X = \sigma_{W_X}$.

We have found that method 1 **does not** provide a reliable estimate of σ_X , **so we recommend method 2**.

Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design

Example 1 – Finding Power

A company has opened a new manufacturing plant and wants to show that the drug produced in the new plant is equivalent to that produced in the older plant. A two-sequence, dual cross-over design will be used to test the equivalence of drugs produced at the two plants.

Researchers have decided to set the equivalence limits for the ratio at 0.80 and 1.25. Past experience leads the researchers to set the COV to 0.40. The significance level is 0.05. The power will be computed assuming that the true ratio is 0.96. Sample sizes between 10 and 80 will be included in the analysis.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design** procedure window by expanding **Means**, then **Cross-Over (Higher-Order) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design**. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Power
Design Type.....	3x2 (Three-Period, Two-Sequence Dual: ABB BAA)
Alpha.....	0.05
N (Total Sample Size).....	10 20 30 40 60 80
RU (Upper Equivalence Limit)	1.25
RL (Lower Equivalence Limit).....	1/RU
R1 (Mean Ratio)	0.96
COV (Coefficient of Variation)	0.40

Annotated Output

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

Numeric Results

Numeric Results of an Equivalence Test of the Mean Ratio in a Three-Period, Two-Sequence Dual Design

Treatment Sequences: ABB | BAA

	Sample Size	Lower Equiv Limit	Upper Equiv Limit	Mean Ratio	Coef of Variation	Alpha
Power	N	RL	RU	R1 ($\mu T/\mu R$)	COV	
0.0000	10	0.800	1.250	0.960	0.4000	0.050
0.3051	20	0.800	1.250	0.960	0.4000	0.050
0.5858	30	0.800	1.250	0.960	0.4000	0.050
0.7483	40	0.800	1.250	0.960	0.4000	0.050
0.9035	60	0.800	1.250	0.960	0.4000	0.050
0.9627	80	0.800	1.250	0.960	0.4000	0.050

Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design

References

Chow, S.C. and Liu, J.P. 1999. Design and Analysis of Bioavailability and Bioequivalence Studies. Marcel Dekker. New York
 Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.
 Chen, K.W.; Chow, S.C.; and Li, G. 1997. 'A Note on Sample Size Determination for Bioequivalence Studies with Higher-Order Crossover Designs.' Journal of Pharmacokinetics and Biopharmaceutics, Volume 25, No. 6, pages 753-765.

Report Definitions

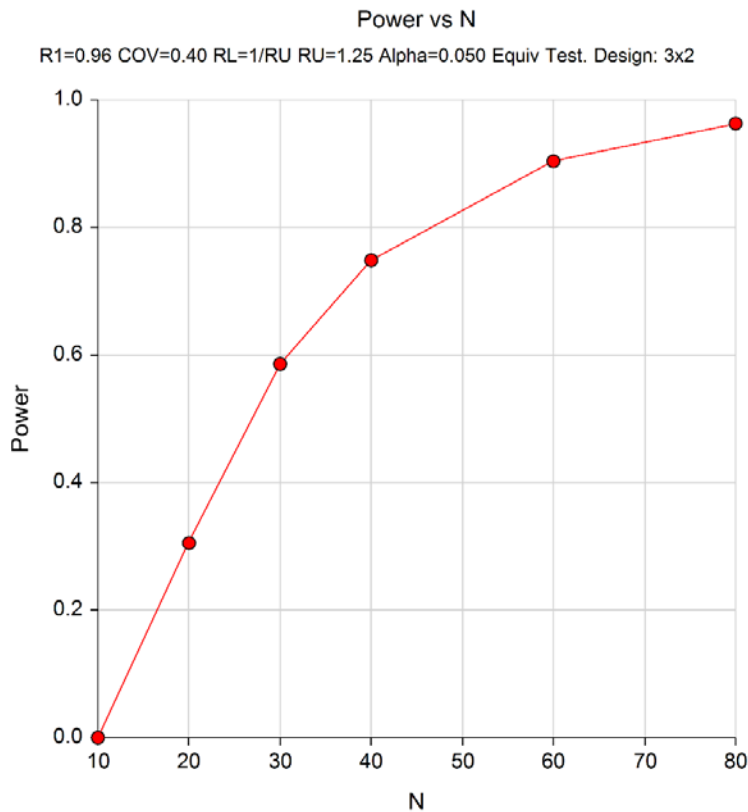
Power is the probability of rejecting non-equivalence when the means are equivalent.
 N is the total number of subjects. They are divided evenly among all sequences.
 RU & RL are the upper and lower equivalence limits. Ratios between these limits are equivalent.
 R1 is the ratio of the means at which the power is computed.
 COV is the coefficient of variation on the original scale.
 Alpha is the probability of rejecting non-equivalence when the means are non-equivalent.

Summary Statements

In an equivalence test of means using two one-sided tests on data drawn from a three-period, two-sequence dual cross-over design, a total sample size of 10 achieves 0% power at a 5% significance level when the mean ratio (μ_T/μ_R) is 0.960, the coefficient of variation on the original (unlogged) scale is 0.4000, and the equivalence limits are 0.800 and 1.250.

This report shows the power for the indicated scenarios. Note that 60 subjects will yield a power of just over 90%.

Plots Section



This plot shows the power versus the sample size.

Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design

Example 2 – Finding Sample Size

Continuing with Example 1, the researchers want to find the exact sample size needed to achieve both 80% power and 90% power.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design** procedure window by expanding **Means**, then **Cross-Over (Higher-Order) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design**. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size (Exact)
Design Type.....	3x2 (Three-Period, Two-Sequence Dual: ABB BAA)
Power.....	0.80 0.90
Alpha.....	0.05
RU (Upper Equivalence Limit)	1.25
RL (Lower Equivalence Limit).....	1/RU
R1 (Mean Ratio)	0.96
COV (Coefficient of Variation)	0.40

Output

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

Numeric Results

Numeric Results of an Equivalence Test of the Mean Ratio in a Three-Period, Two-Sequence Dual Design
 Design: Three-Period, Two-Sequence Dual Cross-Over
 Treatment Sequences: ABB | BAA

	Sample Size N	Lower Equiv Limit RL	Upper Equiv Limit RU	Mean Ratio R1 (μ_T/μ_R)	Coef of Variation COV	Alpha
Power						
0.8026	45	0.800	1.250	0.960	0.4000	0.050
0.9035	60	0.800	1.250	0.960	0.4000	0.050

We note that 60 subjects are needed to achieve 90% power and 45 subjects are needed to achieve at least 80% power.

Example 3 – Validation using Chen et al. (1997)

Chen et al. (1997) page 761 presents a table of sample sizes for various parameter values for Balaam's design. We will reproduce entries from the first and seventeenth lines of the table in which the COV is 10%, the equivalence limits are 0.8 and 1.25, the actual ratio of between the means is 1, the power values are 80% and 90%, and the significance level is 0.05. Chen reports total sample sizes of 16 and 20. We will now setup this example in **PASS**.

The COV entered by Chen is the COV of the logged data. Since **PASS** requires the COV of the original data, we must use the relationship

$$\begin{aligned} COV_y &= \sqrt{e^{\sigma_w^2} - 1} \\ &= \sqrt{e^{0.1^2} - 1} \\ &= \sqrt{e^{0.01} - 1} \\ &= 0.10025 \end{aligned}$$

to obtain the appropriate value of COV.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design** procedure window by expanding **Means**, then **Cross-Over (Higher-Order) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design**. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size (Equal Per Sequence)
Design Type.....	2x4 (Balaam: AA BB AB BA)
Power.....	0.80 0.90
Alpha.....	0.05
RU (Upper Equivalence Limit)	1.25
RL (Lower Equivalence Limit).....	1/RU
R1 (Mean Ratio)	1.0
COV (Coefficient of Variation)	0.10025

Output

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

Numeric Results

Numeric Results of an Equivalence Test of the Mean Ratio in a Two-Period, Four-Sequence (Balaam) Design

Treatment Sequences: AA | BB | AB | BA

	Sample Size	Lower Equiv Limit	Upper Equiv Limit	Mean Ratio	Coef of Variation	Alpha
Power	N	RL	RU	R1 (μ_T/μ_R)	COV	
0.8106	16	0.800	1.250	1.000	0.1003	0.050
0.9085	20	0.800	1.250	1.000	0.1003	0.050

Note that **PASS** has obtained the same samples sizes as Chen et al. (1997).