

Chapter 526

Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design (Log-Normal Data)

Introduction

This procedure calculates power and sample size for inequality tests which use the ratio of the means of a higher-order cross-over design. Measurements are made on individuals that have been randomly assigned to one of several treatment sequences. Only a brief introduction to the subject will be given here. For a comprehensive discussion on the subject, refer to Chen et al. (1997) and Chow et al. (2003).

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 periods (and treatments) 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 sample size 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

Sequence	Period 1	Period 2
1	A	A
2	B	B
3	A	B
4	B	A

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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.

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.

The Statistical Hypotheses

A two-sided hypothesis test comparing the means is given by

$$H_0: \mu_1/\mu_2 = 1 \quad \text{versus} \quad H_1: \mu_1/\mu_2 \neq 1$$

Rejecting H_0 implies that the means are different.

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 scale-less percentages, but differences must be interpreted as actual amounts in their original scale. Also, taking the logarithm of the data can make skewed data closer to normal. Hence, it has become a common practice to take the following steps in hypothesis testing.

1. State the statistical hypotheses in terms of ratios.
2. Transform these into hypotheses about differences by taking logarithms.
3. Analyze the logged data—that is, do the analysis in terms of the difference.
4. Draw the conclusion in terms of the ratio.

In step 2, the statistical hypotheses become

$$H_0: \ln(\mu_1) - \ln(\mu_2) = 0 \quad \text{versus} \quad H_1: \ln(\mu_1) - \ln(\mu_2) \neq 0$$

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.

Coefficient of Variation

The coefficient of variation (COV) is the ratio of the standard deviation to the mean. This parameter is 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

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

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From this relationship, the coefficient of variation of Y can be found to be

$$\begin{aligned} COV_Y &= \frac{\sqrt{\mu_Y^2(e^{\sigma_X^2} - 1)}}{\mu_Y} \\ &= \sqrt{e^{\sigma_X^2} - 1} \\ &= \sqrt{e^{\sigma_W^2} - 1} \end{aligned}$$

where σ_W^2 is the within mean square error from the analysis of variance of the logged data. Solving this relationship for σ_X^2 , the standard deviation of X can be stated in terms of the coefficient of variation of Y as

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

Similarly, the mean of X is

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

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

Test Statistic

The presence of a non-zero difference between the means can be tested using an F-test from an appropriate repeated measures model that may include terms for a sequence effect and/or a carry-over effect. The within mean square error from the ANOVA of the logged data provides an estimate of the within-subject variance.

Power Calculation

The power of a two-sided test is given by Chen, Chow, and Li (1997). The basic formula is

$$\text{Power} = T_V \left[\left(\frac{|\ln(\mu_1) - \ln(\mu_2)|}{\sigma_X \sqrt{b/n}} \right) - t_{V, 1-\alpha/2} \right]$$

where T represents the cumulative t distribution, V and b depend on the design (shown below), σ_X is defined above, and n is the average number of subjects per sequence. Thus, the overall sample size N is given by n times the number of sequences. For a one-sided test, replace $\alpha/2$ with α in the above formula.

The constants V and b depend on the design as follows:

Design Type	Parameters (V, b)
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	$V = 12n - 5, b = 1/4.$

Example 1 – Finding Power

Researchers want to calculate the power of a two-sided, inequality test using data from a three-period, two-sequence, dual cross-over design. They want to investigate sample sizes 5, 10, 15, 20, 35, and 50. They want a sample large enough to detect a mean ratio of 1.25 or 1.5. The significance level is 0.05. Past experience leads the researchers to set the COV to 0.40.

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	Power
Design Type.....	3x2 (Three-Period, Two-Sequence Dual: ABB BAA)
Alternative Hypothesis	Two-Sided
Alpha.....	0.05
N (Total Sample Size).....	5 10 15 20 35 50
R1 (μ_T / μ_R).....	1.25 1.5
COV (Coefficient of Variation).....	0.4

Output

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

Numeric Reports

Numeric Results

Solve For: **Power**
 Design Type: Three-Period, Two-Sequence Dual
 Treatment Sequences: ABB | BAA
 Alternative Hypothesis: Two-Sided

Power	Total Sample Size N	Mean Ratio (μ_T / μ_R) R1	Coefficient of Variation COV	Alpha
0.1070	5	1.25	0.4	0.05
0.2706	10	1.25	0.4	0.05
0.4123	15	1.25	0.4	0.05
0.5344	20	1.25	0.4	0.05
0.7871	35	1.25	0.4	0.05
0.9114	50	1.25	0.4	0.05
0.3091	5	1.50	0.4	0.05
0.7207	10	1.50	0.4	0.05
0.8928	15	1.50	0.4	0.05
0.9611	20	1.50	0.4	0.05
0.9985	35	1.50	0.4	0.05
1.0000	50	1.50	0.4	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 N The total number of subjects. They are divided evenly among all sequences.
 μ_T The treatment mean. It is usually associated with the letter "A" in the design.
 μ_R The reference mean. It is usually associated with the letter "B" in the design.
 R1 The ratio of the means at which the power is computed.
 COV The coefficient of variation on the original scale.
 Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A three-period, two-sequence dual cross-over design (ABB | BAA) will be used to test whether the ratio of means (μ_T / μ_R) is different from 1. The comparison will be made using a two-sided t-test using a log-transformation, with a Type I error rate (α) of 0.05. The coefficient of variation on the original scale is assumed to be 0.4. To detect a ratio of means (μ_T / μ_R) of 1.25, with a total sample size of 5 (allocated equally to the 2 sequences), the power is 0.107.

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Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout- Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	5	7	2
20%	10	13	3
20%	15	19	4
20%	20	25	5
20%	35	44	9
20%	50	63	13

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	The evaluable sample size at which power is computed (as entered by the user). If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. N' is calculated by inflating N using the formula $N' = N / (1 - DR)$, with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. $D = N' - N$.

Dropout Summary Statements

Anticipating a 20% dropout rate, 7 subjects should be enrolled to obtain a final sample size of 5 subjects.

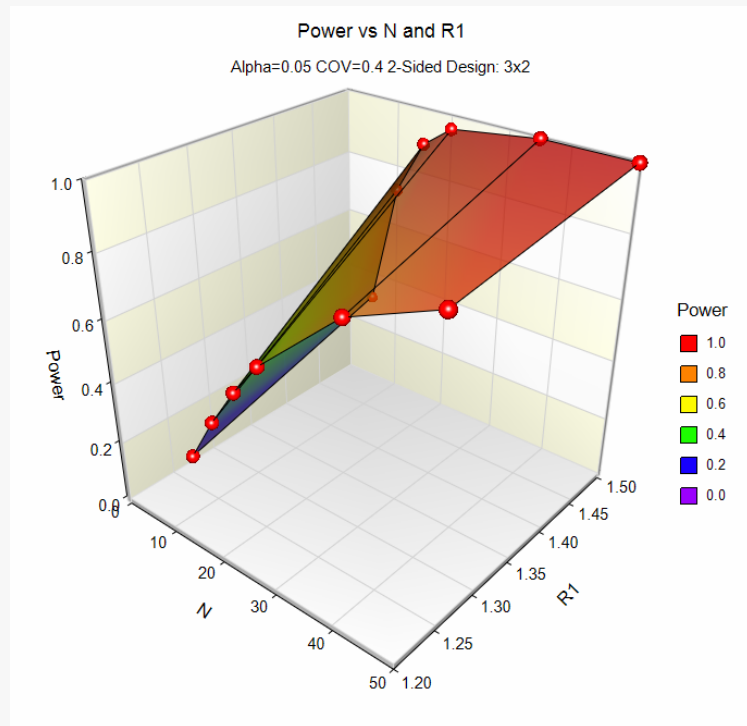
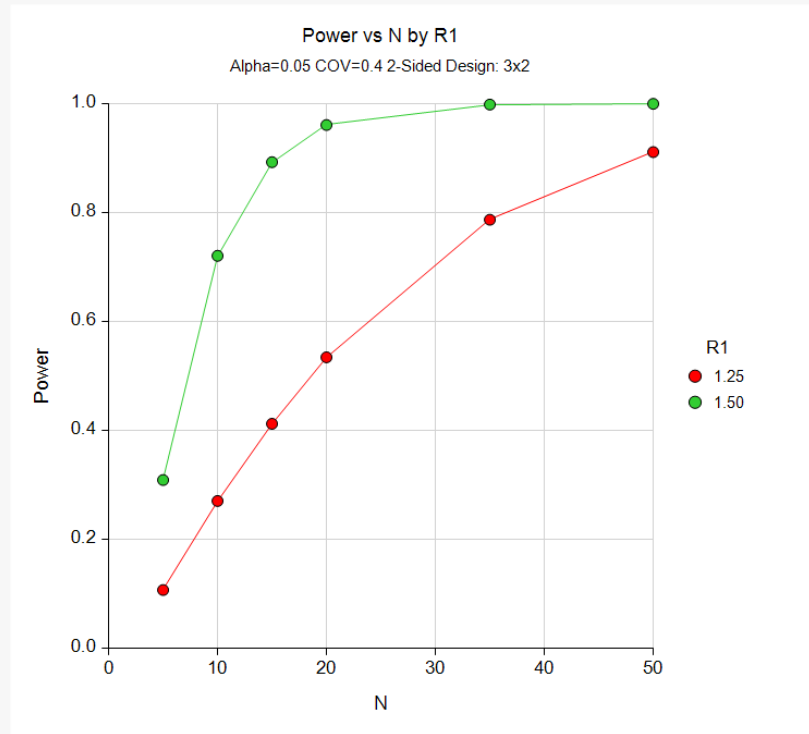
References

- 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., and 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.

This report shows the power for the indicated scenarios.

Plots Section

Plots



These plots show the power versus the sample size.

Example 2 – Finding Sample Size

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

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 (Exact)**
 Design Type..... **3x2 (Three-Period, Two-Sequence Dual: ABB|BAA)**
 Alternative Hypothesis **Two-Sided**
 Power..... **0.90**
 Alpha..... **0.05**
 R1 (μ_T / μ_R)..... **1.25 1.5**
 COV (Coefficient of Variation)..... **0.4**

Output

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

Numeric Results

Solve For: [Sample Size \(Exact\)](#)
 Design Type: Three-Period, Two-Sequence Dual
 Treatment Sequences: ABB | BAA
 Alternative Hypothesis: Two-Sided

Power	Total Sample Size N	Mean Ratio (μ_T / μ_R) R1	Coefficient of Variation COV	Alpha
0.9058	49	1.25	0.4	0.05
0.9121	16	1.50	0.4	0.05

This report shows the sample sizes.

Example 3 – Validation

We will validate this procedure by comparing its results to the *Superiority by a Margin Tests for the Ratio of Two Means in a Higher-Order Cross-Over Design (Log-Normal Data)* procedure which has already been validated. The two routines should achieve the same power when SM is set to zero in that routine.

In the superiority routine, if we set the Design Type to 3x2, Higher Means to Better, Alpha to 0.05, N to 10, SM to 0, Difference to 1.5, and COV to 0.50, the power is computed to be 0.6778.

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 3** 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	Power
Design Type.....	3x2 (Three-Period, Two-Sequence Dual)
Alternative Hypothesis	One-Sided
Alpha.....	0.05
N (Total Sample Size).....	10
R1 (μ_T / μ_R).....	1.5
COV (Coefficient of Variation).....	0.5

Output

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

Numeric Results

Solve For:	Power
Design Type:	Three-Period, Two-Sequence Dual
Treatment Sequences:	ABB BAA
Alternative Hypotheses:	One-Sided

Power	Total Sample Size N	Mean Ratio (μ_T / μ_R) R1	Coefficient of Variation COV	Alpha
0.6778	10	1.5	0.5	0.05

This procedure has also calculated the power to be 0.6778.