Chapter 505

Tests for the Ratio of Two Means in a 2x2 Cross-Over Design (Log-Normal Data)

Introduction

This procedure calculates power and sample size for a 2x2 cross-over design in which the logarithm of the outcome is a continuous normal random variable. This routine deals with the case in which the statistical hypotheses are expressed in terms of ratios of means instead of differences of means.

The details of testing two treatments using data from a 2x2 cross-over design are given in another chapter and they will not be repeated here. If the logarithms of the responses can be assumed to follow a normal distribution, hypotheses stated in terms of the ratio can be transformed into hypotheses about the difference. The details of this analysis are given in Julious (2004). They will only be summarized here.

Testing Using Ratios

It will be convenient to adopt the following specialized notation for the discussion of these tests.

Parameter	PASS Input/Output	Interpretation
μ_T	Not used	*Treatment mean*. This is the treatment (group 1) mean.
μ_R	Not used	*Reference mean*. This is the reference (group 2) mean.
ϕ_0	R0	*Null ratio*. This is the value of $\phi = \mu_T/\mu_R$ under the null hypothesis, H_0.
ϕ	R1	*Actual ratio*. 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 the ratio of these values is needed for power and sample size calculations.

In the two-sided case, the null and alternative hypotheses are

$$H_0: \phi = \phi_0 \quad \text{versus} \quad H_1: \phi \neq \phi_0.$$

The one-sided hypotheses are

$$H_0: \phi \leq \phi_0 \quad \text{versus} \quad H_1: \phi > \phi_0$$

and

$$H_0: \phi \geq \phi_0 \quad \text{versus} \quad H_1: \phi < \phi_0.$$

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. 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.

The details of step 2 for the two-sided null hypothesis are as follows:

$$H_0: \phi = \phi_0 \quad \Rightarrow \quad H_0: \frac{\mu_T}{\mu_R} = \phi_0 \quad \Rightarrow \quad H_0: \ln(\mu_T) - \ln(\mu_R) = \ln(\phi_0)$$

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 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

$$\mu_Y = e^{\mu_X + \frac{\sigma_X^2}{2}}$$

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

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

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

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

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

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.

Power Calculation

As is shown above, the hypotheses can be stated in the original (Y) scale using ratios or the logged (X) scale using differences. In either case, the power and sample size calculations are made using the formulas for testing the difference in two means. These formulas are presented in another chapter and are not duplicated here.

Example 1 – Finding Power

A company has developed a generic drug for treating rheumatism and wants to show that it is better than the standard drug. Responses for either treatment are assumed to follow a lognormal distribution. A 2x2 cross-over design will be used and the logged data will be analyzed using an appropriate analysis of variance. Note that using an analysis of variance instead of a t-test to analyze the data forces the researchers to use two-sided tests.

Past experience leads the researchers to set the COV to 0.50. The significance level is 0.05. The power will be computed for R1 equal to 1.10 and 1.20. Sample sizes between 20 and 220 will be included in the initial analysis.

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**
Alternative Hypothesis	**Two-Sided (H1: R ≠ R0)**
Alpha	**0.05**
N (Total Sample Size)	**20 to 220 by 40**
R0 (Ratio | H0)	**1.0**
R1 (Actual Ratio)	**1.1 1.2**
COV (Coefficient of Variation)	**0.5**

Output

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

Numeric Reports

Numeric Results

Solve For: Power
Test Type: T-Test
Groups: 1 = Treatment, 2 = Reference
Ratio: R = μ1 / μ2 = Treatment Mean / Reference Mean
Hypotheses: H0: R1 = R0 vs. H1: R1 ≠ R0

Power	Total Sample Size N	Ratio R|H0 R0	Ratio Actual R1	Coefficient of Variation COV	Effect Size	Alpha
0.09282	20	1	1.1	0.5	0.143	0.05
0.19246	60	1	1.1	0.5	0.143	0.05
0.29248	100	1	1.1	0.5	0.143	0.05
0.38849	140	1	1.1	0.5	0.143	0.05
0.47766	180	1	1.1	0.5	0.143	0.05
0.55840	220	1	1.1	0.5	0.143	0.05
0.21165	20	1	1.2	0.5	0.273	0.05
0.54738	60	1	1.2	0.5	0.273	0.05
0.77107	100	1	1.2	0.5	0.273	0.05
0.89374	140	1	1.2	0.5	0.273	0.05
0.95369	180	1	1.2	0.5	0.273	0.05
0.98078	220	1	1.2	0.5	0.273	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The total sample size drawn from all sequences. The sample is divided equally among sequences.
R0 The ratio of the means (μ1/μ2) under the null hypothesis, H0.
R1 The ratio of the means (μ1/μ2) at which the power is calculated.
COV The coefficient of variation on the original scale. The value of σ is calculated from this.
Effect Size The effect size = |Ln(R0) - Ln(R1)|/σ.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A 2×2 cross-over design will be used to test whether the ratio of means (μ1 / μ2) is different from 1 (H0: μ1 / μ2 = 1 versus H1: μ1 / μ2 ≠ 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 0.5. To detect a ratio of means (μ1 / μ2) of 1.1, with a total sample size of 20 (allocated equally to the two sequences), the power is 0.09282.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	20	25	5
20%	60	75	15
20%	100	125	25
20%	140	175	35
20%	180	225	45
20%	220	275	55

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 Lokhnygina, Y. (2018) pages 32-33.)
D The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 25 subjects should be enrolled to obtain a final sample size of 20 subjects.

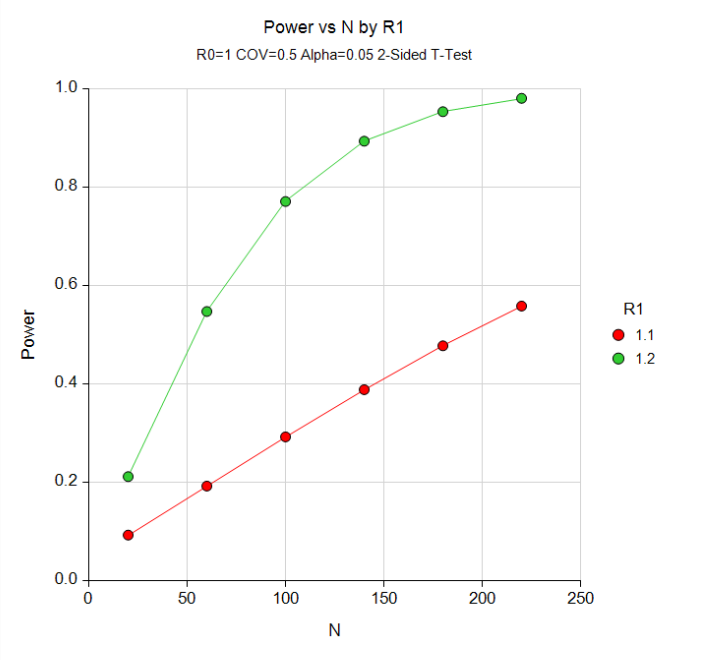
References

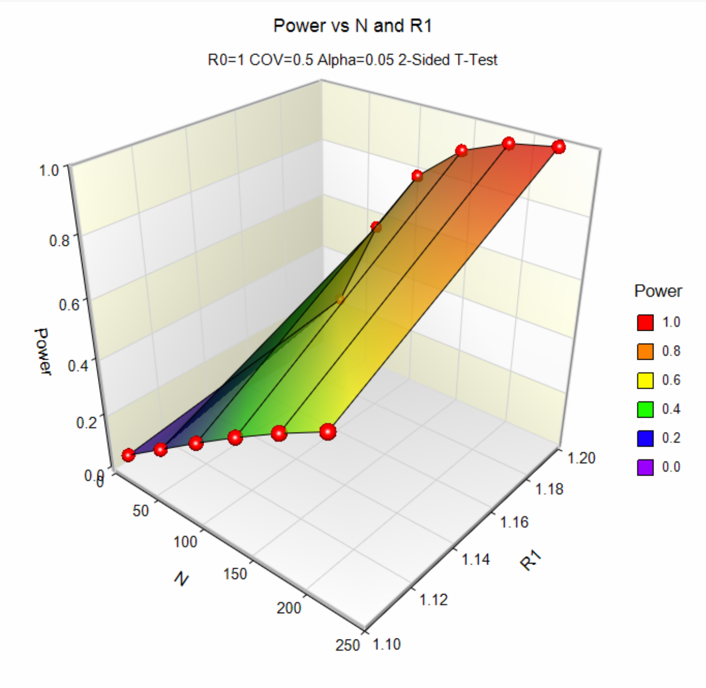
Chow, S.C. and Liu, J.P. 1999. Design and Analysis of Bioavailability and Bioequivalence Studies. Marcel Dekker. New York
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Julious, Steven A. 2004. 'Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data.' Statistics in Medicine, 23:1921-1986.
Senn, Stephen. 2002. Cross-over Trials in Clinical Research. Second Edition. John Wiley & Sons. New York.

This report shows the power for the indicated scenarios.

Plots Section

Plots





These plots show the power versus the sample size for two values of R1.

Example 2 – Validation

We will validate this procedure by showing that it gives the identical results to the regular test on differences—a procedure that has been validated (Tests for the Difference Between Two Means in a 2x2 Cross-Over Design). We will use the same settings as those given in Example 1. Since the output for this example is shown above, all that we need is the output from the procedure that uses differences.

To run the power analysis on differences, we need the values of δ1 (which correspond to R1) and σ_w. The value of δ0 will be zero.

$$\delta 1 = \ln(R1)$$

$$= \ln(1.1)$$

$$= 0.095310$$

$$\delta 1 = \ln(R1)$$

$$= \ln(1.2)$$

$$= 0.182322$$

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

$$= \ln(0.5^2 + 1)$$

$$= 0.472381$$

Setup

If the **Tests for the Difference Between Two Means in a 2x2 Cross-Over Design** 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 2b** settings. 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**
Alternative Hypothesis	**H1: δ ≠ δ0 (Two-Sided)**
Alpha	**0.05**
N (Total Sample Size)	**20 to 220 by 40**
δ0 (Mean Difference|H0)	**0**
δ1 (Mean Difference|H1)	**0.095310 0.182322**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**0.472381**

Output

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

Numeric Results

Solve For: Power
Hypotheses: H0: δ = δ0 vs. H1: δ ≠ δ0

Power	Total Sample Size N	Mean Difference Null δ0	Mean Difference Actual δ1	Standard Deviation σw	Effect Size |δ1 - δ0|/σw	Alpha	Beta
0.09282	20	0	0.09531	0.47238	0.20177	0.05	0.90718
0.19246	60	0	0.09531	0.47238	0.20177	0.05	0.80754
0.29248	100	0	0.09531	0.47238	0.20177	0.05	0.70752
0.38849	140	0	0.09531	0.47238	0.20177	0.05	0.61151
0.47765	180	0	0.09531	0.47238	0.20177	0.05	0.52235
0.55839	220	0	0.09531	0.47238	0.20177	0.05	0.44161
0.21165	20	0	0.18232	0.47238	0.38596	0.05	0.78835
0.54738	60	0	0.18232	0.47238	0.38596	0.05	0.45262
0.77107	100	0	0.18232	0.47238	0.38596	0.05	0.22893
0.89374	140	0	0.18232	0.47238	0.38596	0.05	0.10626
0.95369	180	0	0.18232	0.47238	0.38596	0.05	0.04631
0.98078	220	0	0.18232	0.47238	0.38596	0.05	0.01922

You can compare these power values with those shown above in Example 1 to validate the procedure. You will find that the power values are identical.