Chapter 470

Equivalence Tests for the Ratio of Two Means (Log-Normal Data)

Introduction

This procedure calculates power and sample size of statistical tests for *equivalence* tests from parallel-group design with two groups when the data are assumed to follow a log-normal distribution. This routine deals with the case in which the statistical hypotheses are expressed in terms of mean ratios rather than mean differences.

The details of testing the equivalence of two treatments using a parallel-group design are given in the chapter entitled *Equivalence Tests for Two Means using Differences* and will not be repeated here. If the logarithms of the responses can be assumed to follow a normal distribution, hypotheses about equivalence in terms of the ratio can be transformed into hypotheses about the difference. The details of this analysis are given in Julious (2004).

Note that when the data follow a normal distribution rather than the log-normal distribution, you should use another **PASS** procedure entitled *Equivalence Tests for the Ratio of Two Means (Normal Data)* to obtain more accurate results.

Equivalence Testing Using Ratios

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.

Parameter	PASS Input/Output	Interpretation
μ_T	Not used	*Treatment mean*. This is the treatment mean.
μ_R	Not used	*Reference mean*. This is the mean of a reference population.
R_L, R_U	RL, RU	*Equivalence Limits.* 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	*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.

With $R_L < 1$ and $R_U > 1$, the null hypothesis of non-equivalence is

$$H_0: \phi \leq R_L \ \text{ or } \ \phi \geq R_U.$$

The alternative hypothesis of equivalence is

$$H_1: R_L < \phi < R_U.$$

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 scale-less 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 alternative hypothesis are as follows:

$$H_1: R_L < \phi < R_U \quad \Rightarrow \quad H_1: R_L < \frac{\mu_T}{\mu_R} < R_U \quad \Rightarrow \quad H_1: \ln(R_L) < \ln(\mu_T) - \ln(\mu_R) < \ln(R_U)$$

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.

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 to 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.

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) 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

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

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

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 the power can be analyzed in the transformed (X) scale. For parallel-group designs, $\sigma_X^2 = \sigma_d^2$, the average variance used in the t-test of the logged data.

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. Either way, the power and sample size calculations are made using the formulas for testing the equivalence of the difference in two means. These formulas are presented 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 equivalent to the standard drug. A parallel-group design will be used to test the equivalence of the two drugs.

Researchers have decided to set the lower limit of equivalence at 0.80. Past experience leads the researchers to set the COV to 1.50. The significance level is 0.05. The power will be computed assuming that the true ratio is either 1.00 or 1.05. Sample sizes between 50 and 550 will be included in the 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**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group ....**50 to 550 by 100**
RU (Upper Equivalence Limit) **1/RL**
RL (Lower Equivalence Limit)........................**0.80**
R1 (Actual Ratio) **1.0 1.05**
COV (Coefficient of Variation)........................**1.5**

Output

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

Numeric Reports

Numeric Results
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Solve For: Power
Ratio: R = Treatment Mean / Reference Mean
Hypotheses: H0: R ≤ RL or R ≥ RU   vs.   H1: RL < R < RU
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| | Sample Size | | | Equivalence Limits | | Actual Ratio | Coefficient of Variation | |
Power	N1	N2	N	Lower RL	Upper RU	R1	COV	Alpha
0.00000	50	50	100	0.8	1.25	1.00	1.5	0.05
0.10488	150	150	300	0.8	1.25	1.00	1.5	0.05
0.48431	250	250	500	0.8	1.25	1.00	1.5	0.05
0.71704	350	350	700	0.8	1.25	1.00	1.5	0.05
0.84945	450	450	900	0.8	1.25	1.00	1.5	0.05
0.92208	550	550	1100	0.8	1.25	1.00	1.5	0.05
0.00000	50	50	100	0.8	1.25	1.05	1.5	0.05
0.09731	150	150	300	0.8	1.25	1.05	1.5	0.05
0.43421	250	250	500	0.8	1.25	1.05	1.5	0.05
0.63661	350	350	700	0.8	1.25	1.05	1.5	0.05
0.76018	450	450	900	0.8	1.25	1.05	1.5	0.05
0.83961	550	550	1100	0.8	1.25	1.05	1.5	0.05

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Power   The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1 and N2   The number of items sampled from each population.
N   The total sample size. N = N1 + N2.
RL and RU   The lower and upper equivalence limits, respectively, and are the maximum allowable ratios that still result in equivalence.
R1   The actual ratio of the means at which power is calculated.
COV   The coefficient of variation on the original scale.
Alpha   The probability of rejecting a true null hypothesis.

Summary Statements
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A parallel, two-group design will be used to test whether the Group 1 (treatment) mean is equivalent to the Group 2 (reference) mean, by testing whether the mean ratio (μ1 / μ2) is between the equivalence limits 0.8 and 1.25 (H0: μ1 / μ2 ≤ 0.8 or μ1 / μ2 ≥ 1.25 versus H1: 0.8 < μ1 / μ2 < 1.25). The comparison will be made using two one-sided, two-sample t-tests using a log-transformation, with an overall Type I error rate (α) of 0.05. The coefficient of variation on the original (unlogged) scale for both groups is assumed to be 1.5. To detect a ratio of means (μ1 / μ2) of 1, with a sample size of 50 in Group 1 and 50 in Group 2, the power is 0.
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Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	50	50	100	63	63	126	13	13	26
20%	150	150	300	188	188	376	38	38	76
20%	250	250	500	313	313	626	63	63	126
20%	350	350	700	438	438	876	88	88	176
20%	450	450	900	563	563	1126	113	113	226
20%	550	550	1100	688	688	1376	138	138	276

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.

N1, N2, and N   The evaluable sample sizes at which power is computed (as entered by the user). If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.

N1', N2', and N'   The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' 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.)

D1, D2, and D   The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements

Anticipating a 20% dropout rate, 63 subjects should be enrolled in Group 1, and 63 in Group 2, to obtain final group sample sizes of 50 and 50, respectively.

References

Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.

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.

Phillips, Kem F. 1990. 'Power of the Two One-Sided Tests Procedure in Bioequivalence', Journal of Pharmacokinetics and Biopharmaceutics, Volume 18, No. 2, pages 137-144.

Schuirmann, Donald. 1987. 'A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability', Journal of Pharmacokinetics and Biopharmaceutics, Volume 15, Number 6, pages 657-680.

This report shows the power for the indicated scenarios.

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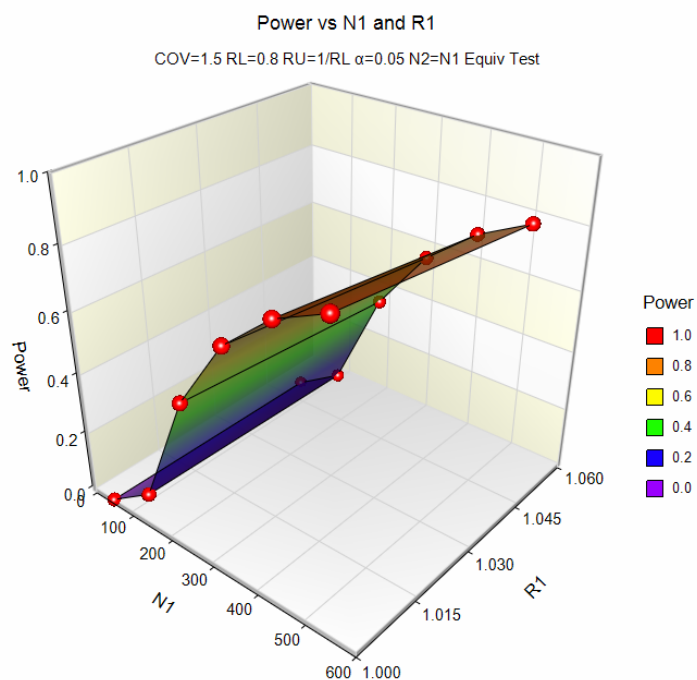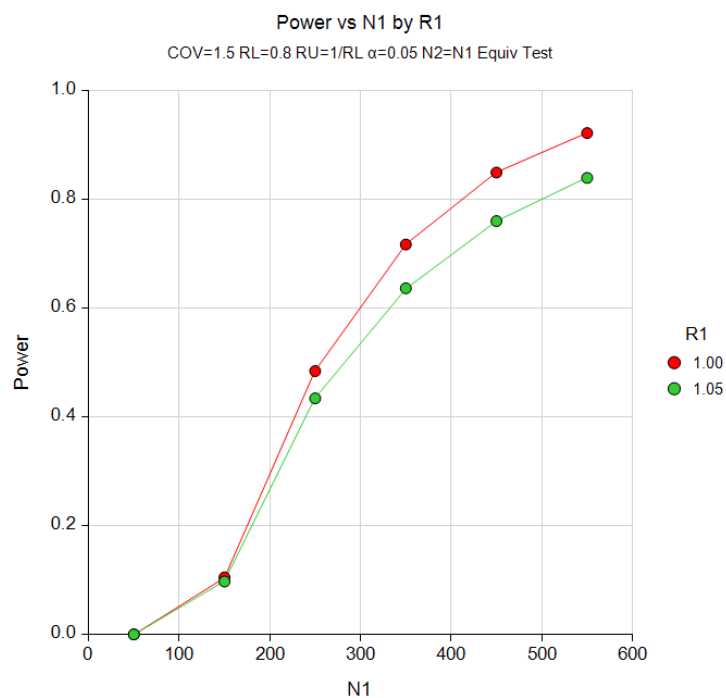
Plots
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These plots show the power versus the sample size for two values of R1.

Example 2 – Validation using Julious (2004)

Julious (2004) page 1971 presents an example of determining the sample size for a parallel-group design in which the actual ratio is 1.0, the coefficient of variation is 0.80, the equivalence limits are 0.80 and 1.25, the power is 90%, and the significance level is 0.05. He calculates the per group sample size to be 216.

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**
Power..**0.90**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
RU (Upper Equivalence Limit) **1/RL**
RL (Lower Equivalence Limit) **0.80**
R1 (Actual Ratio) **1.0**
COV (Coefficient of Variation).......................**0.80**

Output

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

Numeric Results
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Solve For: Sample Size
Ratio: R = Treatment Mean / Reference Mean
Hypotheses: H0: R ≤ RL or R ≥ RU   vs.   H1: RL < R < RU
_____

| Power | | Sample Size | | | Equivalence Limits | | Actual Ratio | Coefficient of Variation | |
| | | | | | Lower | Upper | | | |
Target	Actual	N1	N2	N	RL	RU	R1	COV	Alpha
0.9	0.90044	216	216	432	0.8	1.25	1	0.8	0.05
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PASS also calculates the per group sample size to be 216, which matches Julious' result.