Chapter 513

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

Introduction

This procedure calculates power and sample size of statistical tests for non-unity null tests from a 2x2 cross-over design. 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 non-unity null of 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 the normal distribution, hypotheses about non-unity null 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.

Superiority 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 mean.
μ_R	Not used	*Reference mean*. This is the mean of a reference population.
M_S	SM	*Margin of superiority.* This is a tolerance value that defines the magnitude of difference that is required for practical importance. This may be thought of as the smallest difference from the reference that is considered to be practically significant.
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.

When higher means are better, the hypotheses are arranged so that rejecting the null hypothesis implies that the ratio of the treatment mean to the reference mean is greater than one by at least the margin of superiority. The value of ϕ at which power is calculated must be greater than $\phi_0 = 1 + |M_S|$.

$H_0: \phi \leq 1 + |M_S|$ versus $H_1: \phi > 1 + |M_S|$

$H_0: \phi \leq \phi_0$ versus $H_1: \phi > \phi_0$

When higher means are worse, the hypotheses are arranged so that rejecting the null hypothesis implies that the ratio of the treatment mean to the reference mean is less than one by at least the margin of superiority. The value of ϕ at which power is calculated must be less than $\phi_0 = 1 - |M_S|$.

$H_0: \phi \geq 1 - |M_S|$ versus $H_1: \phi < 1 - |M_S|$

$H_0: \phi \geq \phi_0$ versus $H_1: \phi < \phi_0$

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 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 null hypothesis when higher means are better are as follows:

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

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 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

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

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

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. 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 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 superior to the standard drug by a certain amount. A 2x2 cross-over design will be used to test the superiority of the treatment drug to the reference drug.

Researchers have decided to set the margin of superiority to 0.20. 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 1.40. 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**
Higher Means Are	**Better (H1: R > 1 + SM)**
Alpha	**0.05**
N (Total Sample Size)	**50 to 550 by 100**
SM (Superiority Margin)	**0.2**
R1 (Actual Ratio)	**1.4**
COV (Coefficient of Variation)	**1.5**

Output

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

Numeric Reports

Numeric Results

Solve For:	Power
Groups:	1 = Treatment, 2 = Reference
Ratio:	R = Treatment Mean / Reference Mean
Higher Means Are:	Better
Hypotheses:	H0: R ≤ 1 + SM vs. H1: R > 1 + SM

			Ratio (μ1 / μ2)			
Power	Sample Size N	Superiority Margin SM	Bound R0	Actual R1	Coefficient of Variation COV	Alpha
0.17236	50	0.2	1.2	1.4	1.5	0.05
0.33694	150	0.2	1.2	1.4	1.5	0.05
0.47540	250	0.2	1.2	1.4	1.5	0.05
0.59088	350	0.2	1.2	1.4	1.5	0.05
0.68501	450	0.2	1.2	1.4	1.5	0.05
0.76017	550	0.2	1.2	1.4	1.5	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.
SM	The magnitude of the margin of superiority. Since higher means are better, this value is positive and is the distance above one that is required to be considered superior.
R0	The corresponding superiority margin bound. R0 = 1 + SM.
R1	The mean ratio (treatment/reference) 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 2×2 cross-over design (where higher means are considered to be better) will be used to test whether the treatment 1 mean (μ1) is superior to the treatment 2 mean (μ2) by a margin, by testing whether the ratio of means (μ1 / μ2) is greater than the superiority bound of 1.2 (H0: μ1 / μ2 ≤ 1.2 versus H1: μ1 / μ2 > 1.2). The comparison will be made using a one-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 1.5. To detect a ratio of means (μ1 / μ2) of 1.4, with a total sample size of 50 (allocated equally to the two sequences), the power is 0.17236.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	50	63	13
20%	150	188	38
20%	250	313	63
20%	350	438	88
20%	450	563	113
20%	550	688	138

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, 63 subjects should be enrolled to obtain a final sample size of 50 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.

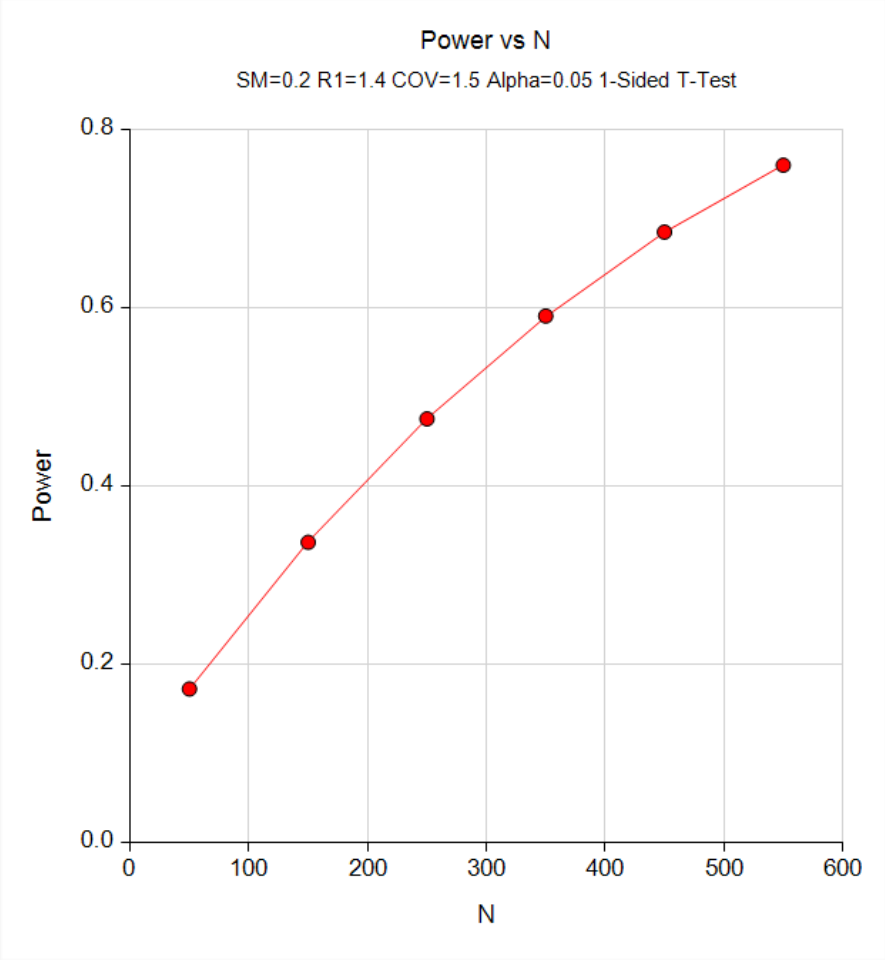
Julious, Steven A. 2004. 'Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data.' Statistics in Medicine, 23:1921-1986.

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. Note that if they want 80% power, they will require a sample of more than 450 subjects.

Plots Section

Plots



This plot shows the power versus the sample size.

Example 2 – Validation

This procedure uses the same mechanics as the *Non-Inferiority Tests for the Ratio of Two Means in a 2x2 Cross-Over Design (Log-Normal Data)* procedure. We refer the user to Example 2 of Chapter 515 for the validation.