

Chapter 515

Non-Inferiority 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-inferiority tests from a 2x2 cross-over design. This routine deals with the case in which the statistical hypotheses are expressed in terms mean ratios rather than mean differences.

The details of testing the non-inferiority 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-inferiority 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.

Non-Inferiority 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	<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.
M_{NI}	NIM	<i>Margin of non-inferiority.</i> This is a tolerance value that defines the maximum amount that is not of practical importance. This is the largest change in the mean ratio from the baseline value (usually one) that is still considered to be trivial.
ϕ	R1	<i>Actual 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 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 minus the margin of non-inferiority. The value of ϕ at which power is calculated must be greater than $\phi_0 = 1 - |M_{NI}|$.

$$\begin{array}{lll}
 H_0: \phi \leq 1 - |M_{NI}| & \text{versus} & H_1: \phi > 1 - |M_{NI}| \\
 H_0: \phi \leq \phi_0 & \text{versus} & H_1: \phi > \phi_0
 \end{array}$$

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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 plus the margin of non-inferiority. The value of ϕ at which power is calculated must be less than $\phi_0 = 1 + |M_{NI}|$.

$$H_0: \phi \geq 1 + |M_{NI}| \quad \text{versus} \quad H_1: \phi < 1 + |M_{NI}|$$

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

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 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:

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

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

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

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

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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.

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 not inferior to standard drug. A 2x2 cross-over design will be used to test the non-inferiority of the treatment drug to the reference drug.

Researchers have decided to set the margin of non-inferiority 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 one. 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 - NIM)
Alpha.....	0.05
N (Total Sample Size).....	50 to 550 by 100
NIM (Non-Inferiority Margin)	0.2
R1 (Actual Ratio)	1.0
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](#)
 Ratio: $R = \text{Treatment Mean} / \text{Reference Mean}$
 Higher Means Are: Better
 Hypotheses: $H_0: R \leq 1 - \text{NIM}$ vs. $H_1: R > 1 - \text{NIM}$

Power	N	Non-Inferiority		Actual Ratio R1	Coefficient of Variation COV	Alpha
		Margin -NIM	Bound R0			
0.26381	50	-0.2	0.8	1	1.5	0.05
0.55053	150	-0.2	0.8	1	1.5	0.05
0.74114	250	-0.2	0.8	1	1.5	0.05
0.85743	350	-0.2	0.8	1	1.5	0.05
0.92415	450	-0.2	0.8	1	1.5	0.05
0.96074	550	-0.2	0.8	1	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.
 -NIM The magnitude and direction of the margin of non-inferiority. Since higher means are better, this value is negative and is the distance below one that is still considered non-inferior.
 R0 The corresponding non-inferiority margin bound. $R_0 = 1 - \text{NIM}$.
 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 2x2 cross-over design (where higher means are considered to be better) will be used to test whether the treatment 1 mean (μ_1) is non-inferior to the treatment 2 mean (μ_2), by testing whether the ratio of means (μ_1 / μ_2) is greater than the non-inferiority bound of 0.8 ($H_0: \mu_1 / \mu_2 \leq 0.8$ versus $H_1: \mu_1 / \mu_2 > 0.8$). 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 (μ_1 / μ_2) of 1, with a total sample size of 50 (allocated equally to the two sequences), the power is 0.26381.

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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%	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 Lohknygina, 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.

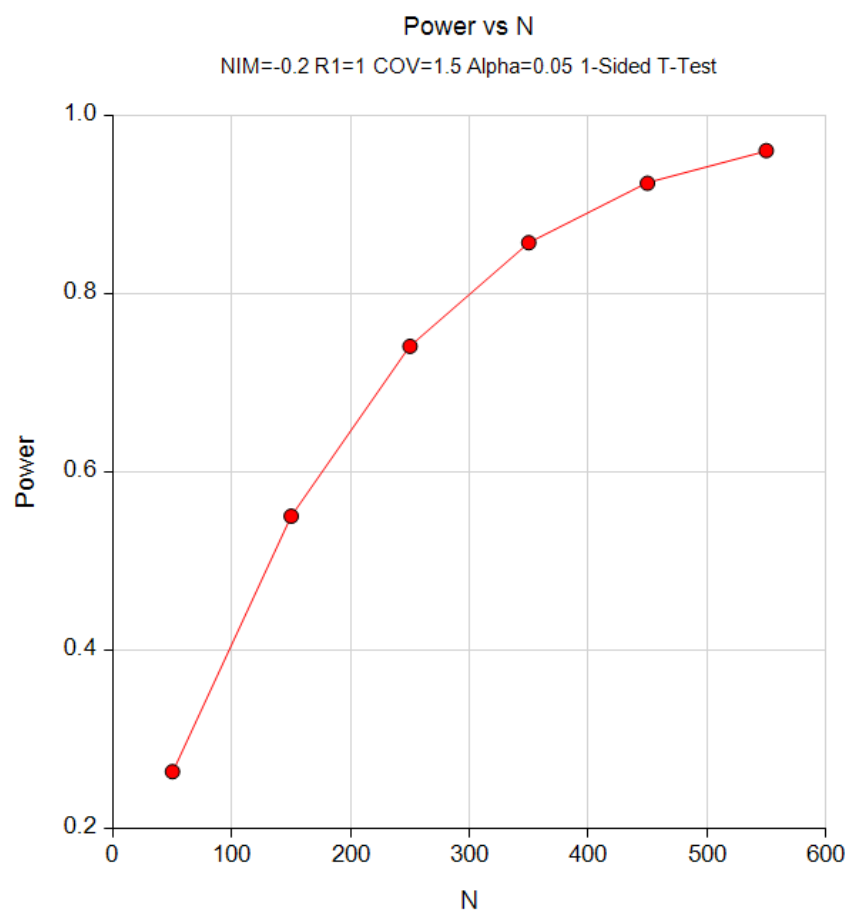
References

- 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 Lohknygina, 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 90% power, they will require a sample of around 450 subjects.

Plots Section

Plots



This plot shows the power versus the sample size.

Example 2 – Validation

We could not find a validation example for this procedure in the statistical literature. Therefore, we will show that this procedure gives the same results as the non-inferiority test on differences—a procedure that has been validated (Non-Inferiority 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, only the output from the procedure that uses differences is shown below.

To run the non-inferiority test on differences, we need the values of NIM and σ_w .

$$NIM' = \ln(1 - NIM)$$

$$= \ln(0.8)$$

$$= 0.223144$$

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

$$= \ln(1.5^2 + 1)$$

$$= 1.085659$$

Setup

If the **Non-Inferiority 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 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: $\delta > -NIM$)
Alpha.....	0.05
N (Total Sample Size).....	50 to 550 by 100
NIM (Non-Inferiority Margin)	0.223144
δ_1 (Actual Difference to Detect).....	0
Standard Deviation Input Type	Enter the Within-Subject Population SD
σ_w (Within-Subject Population SD).....	1.085659

Output

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

Numeric Results

Solve For: **Power**
 Higher Means Are: Better
 Hypotheses: $H_0: \delta \leq -NIM$ vs. $H_1: \delta > -NIM$

Power	Total Sample Size N	Non-Inferiority Margin -NIM	Actual Difference δ_1	Standard Deviation σ_w	Alpha
0.26381	50	-0.22314	0	1.08566	0.05
0.55053	150	-0.22314	0	1.08566	0.05
0.74114	250	-0.22314	0	1.08566	0.05
0.85743	350	-0.22314	0	1.08566	0.05
0.92415	450	-0.22314	0	1.08566	0.05
0.96074	550	-0.22314	0	1.08566	0.05

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.