Chapter 572

Non-Inferiority Tests for the Ratio of Two Means (Normal Data)

Introduction

This procedure calculates power and sample size for *non-inferiority* t-tests from a parallel-groups design with two groups when the data are assumed to follow the normal distribution (so the log transformation is not used). This routine deals with the case in which the statistical hypotheses are expressed in terms of mean ratios instead of mean differences.

The details of this analysis are given in Rothmann, Wiens, and Chan (2012) and, to lesser extent, in Kieser and Hauschke (1999).

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

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	*Treatment mean*. This is the treatment mean.
μ_C	Not used	*Control (Reference) mean*. This is the mean of a reference population.
R_L	RL	*Lower Non-Inferiority Limit*. This is the lower limit for the mean ratio when higher values are 'better'. Values below this amount are assumed to be inferior. Values above this amount are assumed to be non-inferior.
R_U	RU	*Upper Non-Inferiority Limit*. This is the upper limit for the mean ratio when lower values are 'better'. Values above this amount are assumed to be inferior. Values below this amount are assumed to be non-inferior.
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 the non-inferiority limit. The value of ϕ at which power is calculated must be greater than $R_L < \phi$.

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

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 $R_U > \phi$.

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

Coefficient of Variation

The coefficient of variation (CV) is the ratio of the standard deviation to the mean of the control group. This parameter is used to represent the variation in the data. That is, $CV = \frac{\sigma_C}{\mu_C}$.

Power Calculation

Four tests are provided by Rothmann, Wiens, and Chan (2012) for testing non-inferiority based on the mean ratio when the data are assumed to be normally distributed (untransformed). This section will summarize these tests and the associated power and sample size formulas. Rothmann, Wiens, and Chan (2012) provide a much more complete discussion of this topic.

Tests

This section will provide technical details about the four available test statistics that are available for testing non-inferiority using the mean ratio. We begin with some nomenclature.

Suppose a comparison is to be made between two groups: a treatment (T) and a control (C). The response of interest is assumed to follow the normal distribution with (possibly different) means μ_T and μ_C and variances σ_T^2 and σ_C^2. To conduct the comparison, a random sample of N_T and N_C subjects will be obtained for each group. The parameters of the study are presented in terms of the mean ratio $\phi = \mu_T/\mu_C$.

In the results below, let $\lambda = \sigma_T/\sigma_C$, $k = N_T/N_C$, $CV = \sigma_C/\mu_C$, and β be the probability of a type II error.

Assuming that $R_L < 1$, the non-inferiority hypotheses are

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

Four test statistics may be used to test these hypotheses. These are (1) an equal variance t-test, (2) unequal variances large sample z-test, (3) unequal variances Satterthwaite t-test, and (4) unequal variances delta-method z-test.

Equal Variances T-Test

The ratio hypotheses are rearranged as from

$$H_0: \mu_T/\mu_C \leq R_L \text{ versus } H_1: \mu_T/\mu_C > R_L$$

to

$$H_0: \mu_T - R_L\mu_C \leq 0 \text{ versus } H_1: \mu_T - R_L\mu_C > 0$$

The null hypothesis is tested using the test statistic

$$T_1 = \sqrt{\frac{\bar{X}_T - R_L\bar{X}_C}{S\left(\frac{1}{N_T} + \frac{R_L^2}{N_C}\right)}}$$

where $\bar{X}_T$ and $\bar{X}_C$ are the sample means of the two groups and S is the pooled estimate of the standard deviation, σ which is given by

$$S^2 = \frac{(N_T - 1)s_T^2 + (N_C - 1)s_C^2}{N_T - N_C - 2}$$

It is assumed that T_1 is distributed as a central *t* distribution with degrees of freedom given by $N_T + N_C - 2$.

For a specified alternative $\phi = R_1$, T_1 follows the noncentral *t* distribution with $N_T + N_C - 2$ degrees of freedom and noncentrality

$$\left(\frac{\phi - R_L}{CV}\right)\sqrt{\frac{N_C}{\frac{\lambda^2}{k} + R_L^2}}$$

Hence, the power of this test is given by

$$(1 - \beta) = Pr\left(T_1 \geq t_{1-\alpha, N_T+N_C-2} | \phi, R_L, CV\right)$$

Unequal Variances Large Sample Z-Test

The ratio hypotheses are rearranged as from

$$H_0: \mu_T/\mu_C \leq R_L \text{ versus } H_1: \mu_T/\mu_C > R_L$$

to

$$H_0: \mu_T - R_L\mu_C \leq 0 \text{ versus } H_1: \mu_T - R_L\mu_C > 0$$

The null hypothesis is tested using the test statistic

$$T_2 = \frac{\bar{x}_T - R_L\bar{x}_C}{\sqrt{\frac{s_T^2}{N_T} + \frac{s_C^2}{N_C}}}$$

where $\bar{x}_T$ and $\bar{x}_C$ are the sample means of the two groups and s_T and s_C are the estimated of the standard deviations.

It is assumed that T_2 has a standard normal distribution when the null hypothesis is true. When $T_2 > z_\alpha$, the null hypothesis is rejected, and non-inferiority is concluded at a one-sided level of α.

Hence, the approximate power of this test is given by

$$z_\beta = \frac{\mu_T - R_L \mu_C}{\sqrt{\frac{\sigma_T^2}{N_T} + R_L^2 \frac{\sigma_C^2}{N_C}}} - z_\alpha$$

This can be rearranged to give

$$z_\beta = \sqrt{\frac{N_C}{\frac{\lambda^2}{k} + R_L^2}} \left(\frac{\phi - R_L}{CV}\right) - z_\alpha$$

Unequal Variances Satterthwaite T-Test

The ratio hypotheses are rearranged as from

$$H_0: \mu_T/\mu_C \leq R_L \text{ versus } H_1: \mu_T/\mu_C > R_L$$

to

$$H_0: \mu_T - R_L\mu_C \leq 0 \text{ versus } H_1: \mu_T - R_L\mu_C > 0$$

The null hypothesis is tested using the test statistic

$$T_3 = \frac{\bar{x}_T - R_L \bar{x}_C}{\sqrt{\frac{\sigma_T^2}{N_T} + R_L^2 \frac{\sigma_C^2}{N_C}}}$$

where $\bar{x}_T$ and $\bar{x}_C$ are the sample means of the two groups and s_T and s_C are the estimated of the standard deviations.

It is assumed that the distribution of T_3 is a Satterthwaite adjusted central *t* instead of a standard normal when the null hypothesis is true. When $T_3 > -t_{\alpha,v}$, the null hypothesis is rejected, and non-inferiority is concluded at a one-sided level of α. The Satterthwaite degrees of freedom is given by

$$v = \frac{\left[\frac{s_T^2}{N_T} + R_L^2 \frac{s_C^2}{N_C}\right]^2}{\frac{s_T^4}{N_T(N_T - 1)} + R_L^4 \frac{s_C^4}{N_C(N_C - 1)}}$$

The power of this test is given by the non-central *t* distribution with degrees of freedom *v*' estimated by substituting the standard deviations σ_T and σ_C for s_T and s_C in the formula for *v*. The resulting value of *v*' is

$$v' = \frac{\left[\phi^2 + \frac{\lambda^2}{k}\right]^2}{\frac{\lambda^4}{k^2(kN_C - 1)} + \frac{R_L^4}{N_C - 1}}$$

The non-centrality parameter is given by

$$\left(\frac{\phi - R_L}{CV}\right) \sqrt{\frac{N_C}{\frac{\lambda^2}{k} + R_L^2}}$$

Hence, the power of this test is given by

$$(1 - \beta) = Pr\left(T_2 \geq t_{1-\alpha,v'} | \phi, R_L, CV\right)$$

Unequal Variances Delta Method Z-Test

This procedure uses the following ratio hypotheses directly

$$H_0\colon \mu_T/\mu_C \le R_L \text{ versus } H_1\colon \mu_T/\mu_C > R_L$$

The null hypothesis about the ratio is tested using the delta method to determine the distribution of the ratio of two normal means. The unrestricted version of this test statistic is

$$T_4 = \frac{\frac{\bar{X}_T}{\bar{X}_C} - R_L}{\sqrt{\left(\frac{\bar{X}_T}{\bar{X}_C}\right)^2 \left(\frac{s_T^2}{\bar{X}_T^2 N_T} + \frac{s_C^2}{\bar{X}_C^2 N_C}\right)}}$$

The test assumes that T_4 is distributed as a standard normal distribution. Rothmann et al. (2012) state that the accuracy of the standard normal assumption depends on whether T_2 is standard normal and B is close to one where

$$B = \frac{\sqrt{\frac{s_T^2}{N_T} + R_L^2 \frac{s_C^2}{N_C}}}{\sqrt{\frac{s_T^2}{N_T} + \left(\frac{\bar{X}_T}{\bar{X}_C}\right)^2 \frac{s_C^2}{N_C}}}$$

The power of this test is given by

$$z_\beta = \left(\frac{\phi - R_L}{CV}\right) \sqrt{\frac{N_C}{\frac{\lambda^2}{k} + \phi^2}} - z_\alpha$$

where T_4 is now assumed to follow the standard normal distribution mentioned above.

Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to show that it is not inferior to the standard drug. In this case, higher responses are better.

Responses are thought to follow a normal distribution with unequal variances. A parallel-group design will be used, and the data will be analyzed with a Satterthwaite corrected, two-sample t-test.

Researchers have decided to set the non-inferiority limit to 0.80. Past experience leads the researchers to set the CV to 1. The significance level is 0.025 and the power is 0.9. The sample size will be computed assuming that the mean ratio is 0.90, 0.95, or 1.00. The ratio of the two standard deviations is assumed to be 0.6, 0.8, or 1.0.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Higher Means Are	**Better (H1: R > RL, where RL < 1)**
Power	**0.9**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Test Statistic	**Unequal Variances Satterthwaite T-Test**
RL (Lower Non-Inferiority Limit)	**0.8**
R1 (Actual Mean Ratio, μ1 / μ2)	**0.9 0.95 1.0**
CV (Coef of Variation, σ2 / μ2)	**1**
λ (σ Ratio, σ1 / σ2)	**0.6 0.8 1**

Annotated Output

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

Numeric Results

Numeric Results

Ratio (R): μ1 / μ2 = Treatment Mean / Control Mean
Higher Means Are: Better
Hypotheses: H0: R ≤ RL vs. H1: R > RL
Test: Unequal Variances Satterthwaite T-Test

Target Power	Actual Power	N1	N2	N	Lower N.I. Limit RL	Actual Mean Ratio R1	Coef of Var Cntl CV	σ Ratio λ	Alpha
0.9	0.90000	1051	1051	2102	0.8	0.90	1	0.6	0.025
0.9	0.90017	1346	1346	2692	0.8	0.90	1	0.8	0.025
0.9	0.90009	1724	1724	3448	0.8	0.90	1	1.0	0.025
0.9	0.90046	468	468	936	0.8	0.95	1	0.6	0.025
0.9	0.90001	598	598	1196	0.8	0.95	1	0.8	0.025
0.9	0.90033	767	767	1534	0.8	0.95	1	1.0	0.025
0.9	0.90030	264	264	528	0.8	1.00	1	0.6	0.025
0.9	0.90045	337	337	674	0.8	1.00	1	0.8	0.025
0.9	0.90063	432	432	864	0.8	1.00	1	1.0	0.025

References

Rothmann, M.D., Wiens, B.L., and Chan, I.S.F. 2012. Design and Analysis of Non-Inferiority Trials. Taylor & Francis/CRC Press. Boca Raton, Florida.
Kieser, M. and Hauschke, D. 1999. 'Approximate Sample Sizes for Testing Hypotheses about the Ratio and Difference of Two Means.' Journal of Biopharmaceutical Studies, Volume 9, No. 4, pages 641-650.
Hauschke, D., Kieser, M., Diletti, E., Burke, M. 1999. 'Sample Size Determination for Proving Equivalence Based on the Ratio of Two Means for Normally Distributed Data.' Statistics in Medicine, Volume 18, pages 93-105.

Report Definitions

Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.
Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 is the number of subjects sampled from the treatment population.
N2 is the number of subjects sampled from the control population.
N is the total sample size, N1 + N2.
R_L is the non-inferiority limit (or boundary) of the ratio. Since higher means are better, this value is less than one. This is the minimum that the ratio can be and still conclude that the treatment group is not inferior to the control group.
R1 is the mean ratio (treatment/control) at which the power is computed.
CV is the coefficient of variation of the control group. CV = σ2 / μ2.
λ is the ratio of the standard deviations of the treatment and control groups. λ = σ1 / σ2.
Alpha is the probability of rejecting a true null hypothesis.

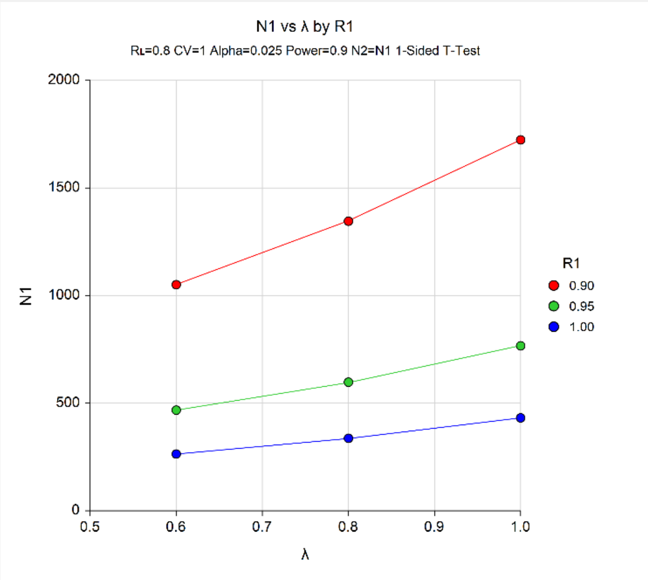
Summary Statements

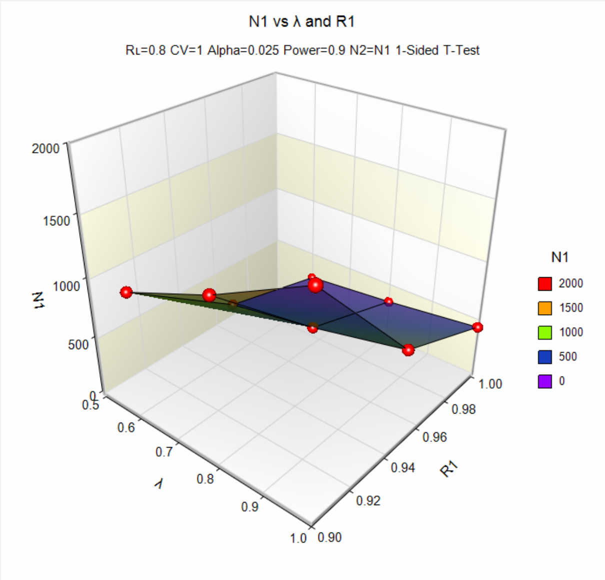
Group sample sizes of 1051 in the treatment group and 1051 in the control group achieve 90% power to detect non-inferiority using a one-sided, unequal variances Satterthwaite t-test which is computed from the original, untransformed, data. The data are assumed to be normally distributed. The non-inferiority limit is 0.8. The ratio of the means at which the power is evaluated is 0.9. The significance level (alpha) of the test is 0.025. The coefficient of variation of the control group is 1. The ratio of the group standard deviations is 0.6.

This report shows the sample size required for the indicated scenarios.

Chart Section

Chart Section





These plots show the sample size for the various scenarios.

Example 2 – Validation using Rothmann (2012)

Rothmann *et al.* (2012) present a table on page 342 in which they calculate several sample sizes. Specifically, they calculate the sample size for the large sample z-test to be 20 in each group.

The non-inferiority limit is 0.75, the CV is 0.3, the significance level is 0.025, the power is 0.9, the SD ratio is 0.5, and mean ratio is 0.95.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Higher Means Are	**Better (H1: R > RL, where RL < 1)**
Power	**0.9**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Test Statistic	**Unequal Variances Large Sample Z-Test**
RL (Lower Non-Inferiority Limit)	**0.75**
R1 (Actual Mean Ratio, μ1 / μ2)	**0.95**
CV (Coef of Variation, σ2 / μ2)	**0.3**
λ (σ Ratio, σ1 / σ2)	**0.5**

Output

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

Numeric Results

Numeric Results

Ratio (R): μ1 / μ2 = Treatment Mean / Control Mean
Higher Means Are: Better
Hypotheses: H0: R ≤ RL vs. H1: R > RL
Test: Unequal Variances Large Sample Z-Test

Target Power	Actual Power	N1	N2	N	Lower N.I. Limit RL	Actual Mean Ratio R1	Coef of Var Cntl CV	σ Ratio λ	Alpha
0.9	0.91111	20	20	40	0.75	0.95	0.3	0.5	0.025

PASS also calculates the sample size in each group to be 20.