Chapter 128

Tests for the Ratio of Two Means (Normal Data)

Introduction

This procedure calculates power and sample size for t-tests and z-tests from a parallel-groups design with two groups when <u>the data are assumed to follow the normal distribution</u> (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 a 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 *Tests for the Ratio of Two Means (Log-Normal Data)* to obtain more accurate results.

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_1	Not used	*Group 1 mean*. This is the treatment mean.
μ_2	Not used	*Group 2 mean*. This is the control mean.
R_0	R0	*Null ratio*. This is the value of $R = \mu_1/\mu_2$ under the null hypothesis, H_0.
R	R1	*Actual ratio*. This is the value of $R = \mu_1/\mu_2$ at which the power is calculated.

Note that the actual values of μ_1 and μ_2 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

$$H_0: R = R_0 \quad \text{versus} \quad H_1: R \neq R_0.$$

The one-sided hypotheses are

$$H_0: R \leq R_0 \quad \text{versus} \quad H_1: R > R_0$$

and

$$H_0: R \geq R_0 \quad \text{versus} \quad H_1: R < R_0.$$

Coefficient of Variation

The coefficient of variation (CV) is the ratio of the standard deviation to the mean of group 2, the control group. This parameter is used to represent the variation in the data. That is, $CV = \frac{\sigma_2}{\mu_2}$.

Power Calculation

We will use three of the four tests that are provided by Rothmann, Wiens, and Chan (2012) for testing the mean ratio directly 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 three available test statistics that are available. We begin with some nomenclature.

Suppose a comparison is to be made between two groups labelled "1" and "2". When desired, you can think of group 1 as the treatment group and group 2 as the control group. The response of interest is assumed to follow the normal distribution with (possibly different) means μ_1 and μ_2 and variances σ_1^2 and σ_2^2. To conduct the comparison, a random sample of N_1 and N_2 subjects will be obtained for each group. The parameters of the study are presented in terms of the mean ratio $R = \mu_1/\mu_2$.

In the results below, let $\lambda = \sigma_1/\sigma_2$, $k = N_1/N_2$, $CV = \sigma_2/\mu_2$, and β be the probability of a type II error.

The three test statistics are (1) an equal variance t-test, (2) unequal variances large sample z-test, and (3) unequal variances Satterthwaite t-test.

Equal Variances T-Test

The two-sided, ratio hypotheses are rearranged as from

$$H_0:\frac{\mu_1}{\mu_2} = R_0 \quad \text{versus} \quad H_1:\frac{\mu_1}{\mu_2} \neq R_0$$

to

$$H_0: \mu_1 - R_0\mu_2 = 0 \quad \text{versus} \quad H_1: \mu_1 - R_0\mu_2 \neq 0$$

The null hypothesis is tested using the test statistic

$$T_1 = \sqrt{\frac{\bar{X}_1 - R_0\bar{X}_2}{S\left(\frac{1}{N_1} + \frac{R_0^2}{N_2}\right)}}$$

where $\bar{X}_1$ and $\bar{X}_2$ are the sample means of the two groups and S is the pooled estimate of the standard deviation, σ which is given by

$$S^2 = \frac{(N_1 - 1)s_1^2 + (N_2 - 1)s_2^2}{N_1 - N_2 - 2}$$

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It is assumed that T_1 is distributed as a central t distribution with degrees of freedom given by $N_1 + N_2 - 2$.

For a specified alternative $R = R_1$, T_1 follows the noncentral t distribution with $N_1 + N_2 - 2$ degrees of freedom and noncentrality

$$\left(\frac{R - R_0}{CV}\right)\sqrt{\frac{N_2}{\frac{\lambda^2}{k} + R_0^2}}$$

Hence, the power of this test is given by

$$(1 - \beta) = Pr\left(T_1 \geq t_{1-\alpha/2, N_1+N_2-2} | R, R_0, CV\right)$$

Unequal Variances Large Sample Z-Test

The two-sided, ratio hypotheses are rearranged as from

$$H_0 : \frac{\mu_1}{\mu_2} = R_0 \quad \text{versus} \quad H_1 : \mu_1/\mu_2 \neq R_0$$

to

$$H_0 : \mu_1 - R_0\mu_2 = 0 \quad \text{versus} \quad H_1 : \mu_1 - R_0\mu_2 \neq 0$$

The null hypothesis is tested using the test statistic

$$T_2 = \frac{\bar{x}_1 - R_0\bar{x}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

where $\bar{x}_1$ and $\bar{x}_2$ are the sample means of the two groups and s_1 and s_2 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 $|T_2| > z_{1-\alpha/2}$, the null hypothesis is rejected, and inequality is concluded at a two-sided level of α.

Hence, the approximate power of this test is given by

$$z_\beta = \frac{\mu_1 - R_0\mu_2}{\sqrt{\frac{\sigma_1^2}{N_1} + R_0^2\frac{\sigma_2^2}{N_2}}} - z_{\alpha/2}$$

This can be rearranged to give

$$z_\beta = \sqrt{\frac{N_2}{\frac{\lambda^2}{k} + R_0^2}}\left(\frac{R - R_0}{CV}\right) - z_{\alpha/2}$$

Unequal Variances Satterthwaite T-Test

The two-sided, ratio hypotheses are rearranged as from

$$H_0: \frac{\mu_1}{\mu_2} = R_0 \quad \text{versus} \quad H_1: \mu_1/\mu_2 \neq R_0$$

to

$$H_0: \mu_1 - R_0\mu_2 = 0 \quad \text{versus} \quad H_1: \mu_1 - R_0\mu_2 \neq 0$$

The null hypothesis is tested using the test statistic

$$T_3 = \frac{\bar{x}_1 - R_0\bar{x}_2}{\sqrt{\frac{\sigma_1^2}{N_1} + R_0^2 \frac{\sigma_2^2}{N_2}}}$$

where $\bar{x}_1$ and $\bar{x}_2$ are the sample means of the two groups and s_1 and s_2 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 $|T_3| > t_{1-\alpha/2,v}$, the null hypothesis is rejected, and inequality is concluded at a two-sided level of α. The Satterthwaite degrees of freedom is given by

$$v = \frac{\left[\frac{s_1^2}{N_1} + R_0^2 \frac{s_2^2}{N_2}\right]^2}{\frac{s_1^4}{N_1(N_1-1)} + R_0^4 \frac{s_2^4}{N_2(N_2-1)}}$$

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_1 and σ_2 for s_1 and s_2 in the formula for v. The resulting value of v is

$$v' = \frac{\left[R^2 + \frac{\lambda^2}{k}\right]^2}{\frac{\lambda^4}{k^2(kN_2-1)} + \frac{R_0^4}{N_2-1}}$$

The non-centrality parameter is given by

$$\left(\frac{R - R_0}{CV}\right)\sqrt{\frac{N_2}{\frac{\lambda^2}{k} + R_0^2}}$$

Hence, the power of this test is given by

$$(1 - \beta) = Pr\left(|T_2| \geq t_{1-\alpha/2,v'}|R, R_0, CV\right)$$

Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to show that it is different from the standard drug. 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 R0 = 1, R1 = 0.7, 0.8, or 0.9. Past experience leads the researchers to set the CV to 1. The significance level is 0.05 and the power is 0.9. The ratio of the two standard deviations is assumed to be 0.5 or 1.0.

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 ....**Sample Size**
Alternative Hypothesis ....**Two-Sided (H1: R ≠ R0)**
Test Type..**Unequal Variances Satterthwaite T-Test**
Power..**0.90**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
R0 (Ratio | H0)..**1.0**
R1 (Ratio | H1)..**0.7 0.8 0.9**
CV (Coef of Variation, $\sigma 2 / \mu 2$).......................**1**
λ (Ratio of σ's, $\sigma 1 / \sigma 2$) **0.5 1**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Groups: 1 = Treatment, 2 = Control
Ratio: R = μ_1 / μ_2
Hypotheses: H0: R = R0   vs.   H1: R ≠ R0
Test: Unequal Variances Satterthwaite T-Test

Power		Sample Size			Ratio of Means		Control Group Coefficient of Variation	Ratio of σ's	
Target	Actual	N1	N2	N	Ratio | H0 R0	Ratio | H1 R1	CV	λ	Alpha
0.9	0.90146	148	148	296	1	0.7	1	0.5	0.05
0.9	0.90065	235	235	470	1	0.7	1	1.0	0.05
0.9	0.90029	330	330	660	1	0.8	1	0.5	0.05
0.9	0.90022	526	526	1052	1	0.8	1	1.0	0.05
0.9	0.90006	1314	1314	2628	1	0.9	1	0.5	0.05
0.9	0.90004	2102	2102	4204	1	0.9	1	1.0	0.05

Target Power   The desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null
               hypothesis.
Actual Power   The power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than
               the target power.
N1   The number of subjects sampled from the treatment population.
N2   The number of subjects sampled from the control population.
N   The total sample size. N = N1 + N2.
R0   The ratio of means assumed by the null hypothesis. R = μ_1 / μ_2.
R1   The ratio of means assumed by the alternative hypothesis. R = μ_1 / μ_2.
CV   The coefficient of variation of group 2, the control group. CV = σ_2 / μ_2.
λ   The ratio of the standard deviations of groups 1 and 2. λ = σ_1 / σ_2.
Alpha   The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design will be used to test whether the mean ratio (R = μ_1 / μ_2) is different from 1 (H0: R = 1 versus H1: R ≠ 1). The comparison will be made using the original (untransformed) data with a two-sample, two-sided, unequal variances Satterthwaite t-test, with a Type I error rate (α) of 0.05. The ratio of the group standard deviations (σ_1 / σ_2) is assumed to be 0.5, and the coefficient of variation of the control group (σ_2 / μ_2) is assumed to be 1. To detect a mean ratio of 0.7 with 90% power, the number of subjects needed will be 148 in Group 1 (treatment), and 148 in Group 2 (control).

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	148	148	296	185	185	370	37	37	74
20%	235	235	470	294	294	588	59	59	118
20%	330	330	660	413	413	826	83	83	166
20%	526	526	1052	658	658	1316	132	132	264
20%	1314	1314	2628	1643	1643	3286	329	329	658
20%	2102	2102	4204	2628	2628	5256	526	526	1052

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. 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. After solving for N1 and N2, 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, 185 subjects should be enrolled in Group 1, and 185 in Group 2, to obtain final group sample sizes of 148 and 148, respectively.

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.

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

Plots Section
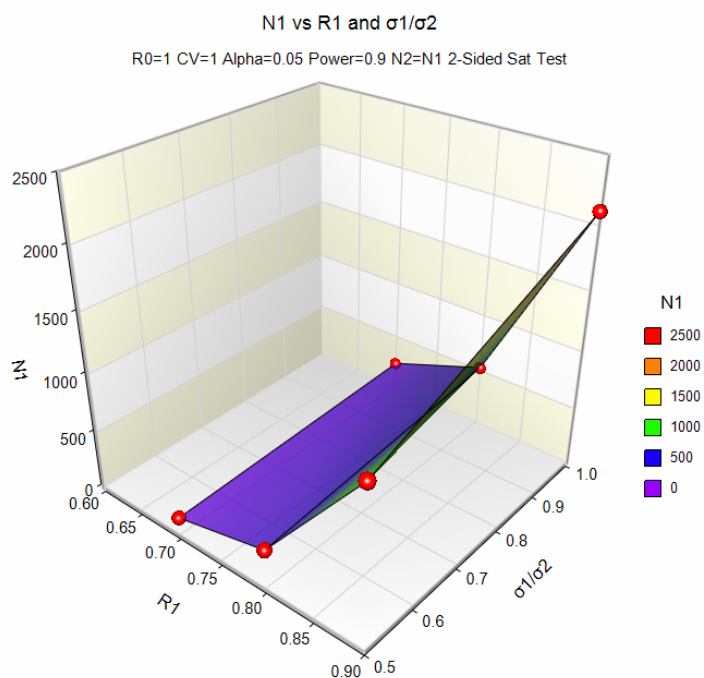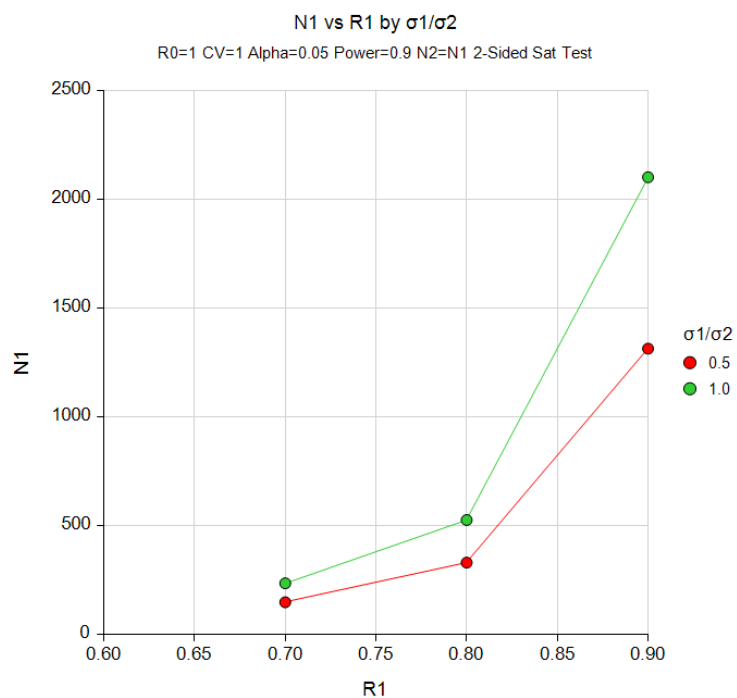
Plots

These plots show the sample size for the various scenarios.

Example 2 – Validation using Rothmann et al. (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 for a one-sided test.

The R0 is 0.75, R1 is 0.95, CV is 0.3, alpha is 0.025, power is 0.9, and SD ratio is 0.5.

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**
Alternative Hypothesis ....**One-Sided (H1: R > R0)**
Test Type..**Unequal Variances Large Sample Z-Test**
Power...**0.90**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
R0 (Ratio | H0)...**0.75**
R1 (Ratio | H1)...**0.95**
CV (Coef of Variation, $\sigma2 / \mu2$).......................**0.3**
λ (Ratio of σ's, $\sigma1 / \sigma2$) **0.5**

Output

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

Numeric Results
_____
Solve For: Sample Size
Groups: 1 = Treatment, 2 = Control
Ratio: R = $\mu1 / \mu2$
Hypotheses: H0: R ≤ R0   vs.   H1: R > R0
Test: Unequal Variances Large Sample Z-Test
_____

Power		Sample Size			Ratio of Means		Control Group Coefficient of Variation	Ratio of σ's	
Target	Actual	N1	N2	N	Ratio | H0 R0	Ratio | H1 R1	CV	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. Thus, the procedure is validated.