Chapter 453

Superiority by a Margin Tests for the Ratio of Two Means (Log-Normal Data)

Introduction

This procedure calculates power and sample size for *superiority by a margin* t-tests from a parallel-groups design in which the logarithm of the outcome is a continuous normal random variable. 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 testing the superiority (or non-unity null) hypothesis of two treatments using data from a two-group design are given in another chapter and they will not be repeated here. If the logarithm of the response can be assumed to follow a normal distribution, 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 $\phi_0 = 1 - |M_S|$.

$$H_0: \phi \geq 1 - |M_S| \qquad \text{versus} \qquad H_1: \phi < 1 - |M_S|$$

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

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 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. In either case, the power and sample size calculations are made using the formulas for testing 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 drug for treating rheumatism and wants to show that it is superior to the standard drug by a certain amount. Responses following either treatment are known to follow a log normal distribution. A parallel-group design will be used, and the logged data will be analyzed with a two-sample t-test.

Researchers have decided to set the margin of superiority at 0.20. Past experience leads the researchers to set the COV to 1.50. The significance level is 0.025. The power will be computed assuming that the true ratio is either 1.30 or 1.40. Sample sizes between 100 and 1000 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**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group ....**100 to 1000 by 100**
SM (Superiority Margin) **0.2**
R1 (Actual Ratio) **1.3 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

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Solve For:	Power
Groups:	1 = Treatment, 2 = Reference
Ratio:	R = Treatment Mean / Reference Mean = μ1 / μ2
Higher Means Are:	Better
Hypotheses:	H0: R ≤ 1 + SM vs. H1: R > 1 + SM

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	Sample Size			Superiority Margin	Ratio (μ1 / μ2)		Coefficient of Variation	
					Bound	Actual		
Power	N1	N2	N	SM	R0	R1	COV	Alpha
0.07477	100	100	200	0.2	1.2	1.3	1.5	0.025
0.11039	200	200	400	0.2	1.2	1.3	1.5	0.025
0.14493	300	300	600	0.2	1.2	1.3	1.5	0.025
0.17994	400	400	800	0.2	1.2	1.3	1.5	0.025
0.21389	500	500	1000	0.2	1.2	1.3	1.5	0.025
0.24762	600	600	1200	0.2	1.2	1.3	1.5	0.025
0.28099	700	700	1400	0.2	1.2	1.3	1.5	0.025
0.31390	800	800	1600	0.2	1.2	1.3	1.5	0.025
0.34624	900	900	1800	0.2	1.2	1.3	1.5	0.025
0.37791	1000	1000	2000	0.2	1.2	1.3	1.5	0.025
0.16832	100	100	200	0.2	1.2	1.4	1.5	0.025
0.29339	200	200	400	0.2	1.2	1.4	1.5	0.025
0.41147	300	300	600	0.2	1.2	1.4	1.5	0.025
0.51938	400	400	800	0.2	1.2	1.4	1.5	0.025
0.61229	500	500	1000	0.2	1.2	1.4	1.5	0.025
0.69123	600	600	1200	0.2	1.2	1.4	1.5	0.025
0.75687	700	700	1400	0.2	1.2	1.4	1.5	0.025
0.81046	800	800	1600	0.2	1.2	1.4	1.5	0.025
0.85355	900	900	1800	0.2	1.2	1.4	1.5	0.025
0.88775	1000	1000	2000	0.2	1.2	1.4	1.5	0.025

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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.
SM	The magnitude of the margin of superiority. Since higher means are better, this value is positive and is the distance above one that the ratio must be for the treatment group to be considered superior.
R0	The superiority bound on the ratio corresponding to SM. 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

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A parallel two-group design will be used to test whether the Group 1 (treatment) mean is superior to the Group 2 (reference) mean by a margin, with a superiority margin (difference from a ratio of 1) of 0.2 (H0: μ1 / μ2 ≤ 1.2 versus Ha: μ1 / μ2 > 1.2). The comparison will be made using a one-sided, two-sample t-test using a log-transformation, with a Type I error rate (α) of 0.025. The coefficient of variation on the original scale for both groups is assumed to be 1.5. To detect a ratio of means (μ1 / μ2) of 1.3, with a sample size of 100 in Group 1 and 100 in Group 2, the power is 0.07477.

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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%	100	100	200	125	125	250	25	25	50
20%	200	200	400	250	250	500	50	50	100
20%	300	300	600	375	375	750	75	75	150
20%	400	400	800	500	500	1000	100	100	200
20%	500	500	1000	625	625	1250	125	125	250
20%	600	600	1200	750	750	1500	150	150	300
20%	700	700	1400	875	875	1750	175	175	350
20%	800	800	1600	1000	1000	2000	200	200	400
20%	900	900	1800	1125	1125	2250	225	225	450
20%	1000	1000	2000	1250	1250	2500	250	250	500

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, 125 subjects should be enrolled in Group 1, and 125 in Group 2, to obtain final group sample sizes of 100 and 100, respectively.

References

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.

This report shows the power for the indicated scenarios.

Plots Section

Plots

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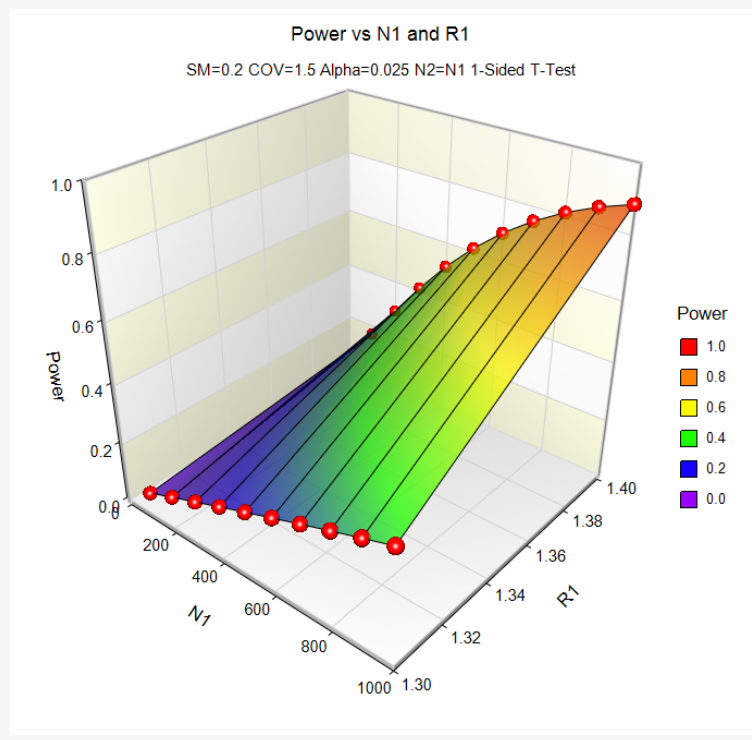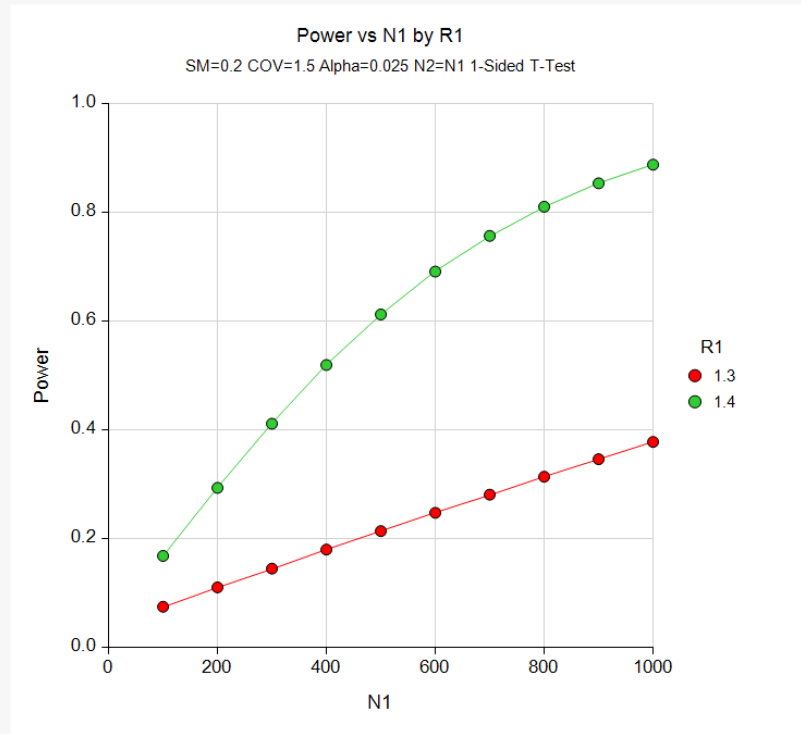
These plots show the power versus the sample size for two values of R1.

Example 2 – Validation using Another Procedure

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 test on differences (**Two-Sample T-Tests for Superiority by a Margin Assuming Equal Variance**)—a procedure that has been validated. We will use the same settings as those given in Example 1 except that the sample size per group will only be 1000 and R1 will only be 1.3. Since the output for this example is shown above, all that we need is the output from the procedure that uses differences.

To run the superiority test on differences, we need the values of SM, δ, and σ.

$$SM = \ln(1 + SM)$$

$$= \ln(1.2)$$

$$= 0.182322$$

$$\delta = \ln(R1)$$

$$= \ln(1.3)$$

$$= 0.262364$$

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

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

$$= 1.085659$$

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Two-Sample T-Tests for Superiority by a Margin Assuming Equal Variance** procedure window. You may then make the appropriate entries as listed below, or open **Example 2b** by going to the **File** menu and choosing **Open Example Template**.

Design Tab

Solve For ....**Power**
Higher Means Are..**Better (H1: δ > SM)**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **1000**
SM (Superiority Margin) **0.182322**
δ (Actual Difference to Detect).......................**0.262364**
σ (Standard Deviation)...................................**1.085659**

Output

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

Numeric Results

Solve For: Power
Test Type: Two-Sample Equal-Variance T-Test
Difference: $\delta = \mu_1 - \mu_2 = \mu_T - \mu_R$
Higher Means Are: Better
Hypotheses: H0: $\delta \leq$ SM   vs.   H1: $\delta >$ SM

	Sample Size			Superiority Margin	Mean Difference	Standard Deviation	
Power	**N1**	**N2**	**N**	**SM**	**δ**	**σ**	**Alpha**
0.3779	1000	1000	2000	0.182322	0.262364	1.085659	0.025

We will now generate this value using the current procedure.

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 ....**Power**
Higher Means Are..**Better**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **1000**
SM (Superiority Margin) **0.2**
R1 (Actual Ratio) **1.3**
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 = μ_1 / μ_2
Higher Means Are: Better
Hypotheses: H0: R ≤ 1 + SM   vs.   H1: R > 1 + SM

| | Sample Size | | | Superiority Margin | Ratio (μ_1 / μ_2) | | Coefficient of Variation | |
| | | | | | Bound | Actual | | |
Power	N1	N2	N	SM	R0	R1	COV	Alpha
0.37791	1000	1000	2000	0.2	1.2	1.3	1.5	0.025

The power value is the same (within rounding) so the procedure is validated.