Chapter 137

Non-Inferiority Tests for the Ratio of Two Variances

Introduction

This procedure calculates power and sample size of *non-inferiority* tests of (total = between + within) variances from a two-group, parallel design. This routine deals with the case in which the statistical hypotheses are expressed in terms of the ratio of the variances.

Technical Details

This procedure uses the formulation given in Chow, Shao, Wang, and Lokhnygina (2018), pages 217 - 220.

Suppose x_{ij} is the response of the *i*th group (*i* = 1, 2) and *j*th subject (*j* = 1, ..., *Ni*). The model analyzed in this procedure is

$$x_{ijk} = \mu_i + e_{ij}$$

where μ_i is the treatment effect and e_{ij} is the between-subject error term which is normally distributed with mean 0 and variance $V_i = \sigma_{Bi}^2$. Unbiased estimators of these variances are given by

$$\hat{V}_i = \frac{1}{N_i - 1}\sum_{j=1}^{N_i}\left(x_{ij} - \bar{x}_i\right)^2$$

$$\bar{x}_i = \frac{1}{N_i}\sum_{j=1}^{N_i} x_{ij}$$

A common test statistic to compare variabilities in the two groups is $T = \hat{V}_1/\hat{V}_2$. Under the usual normality assumptions, *T* is distributed as an *F* distribution with degrees of freedom $N_1 - 1$ and $N_2 - 1$.

Testing Non-Inferiority

The following hypotheses are usually used to test for non-inferiority

$$H_0: \sigma_1^2/\sigma_2^2 \geq R0 \quad \text{versus} \quad H_1: \sigma_1^2/\sigma_2^2 < R0,$$

where *R0* is the non-inferiority limit.

The corresponding test statistic is $T = (\hat{V}_1/\hat{V}_2)/R0$.

Power

The power of this combination of tests is given by

$$\text{Power} = \text{P}\left(F < \left(\frac{R0}{R1}\right) F_{\alpha,N_1-1,N_2-1}\right)$$

where *F* is the common F distribution with the indicated degrees of freedom, α is the significance level, and *R1* is the value of the variance ratio stated by the alternative hypothesis. Lower quantiles of F are used in the equation.

A simple binary search algorithm can be applied to this power function to obtain an estimate of the necessary sample size.

Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to show that it is non-inferior to the standard drug in terms of the variances. A parallel-group design will be used to test the non-inferiority.

Company researchers set the non-inferiority limit to 1.5, the significance level to 0.05, the power to 0.90, and the actual variance ratio values between 0.8 and 1.3. They want to investigate the range of required sample size values assuming that the two group sample sizes are equal.

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**
Power... **0.90**
Alpha.. **0.05**
Group Allocation .... **Equal (N1 = N2)**
R0 (Non-Inferiority Variance Ratio)................ **1.5**
R1 (Actual Variance Ratio) **0.8 0.9 1 1.2 1.3**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Hypotheses: H0: $\sigma^2 1/\sigma^2 2 \geq R0$ vs. H1: $\sigma^2 1/\sigma^2 2 < R0$

Power		Sample Size			Variance Ratio		
Target	Actual	N1	N2	N	Non-Inferiority R0	Actual R1	Alpha
0.9	0.9013	89	89	178	1.5	0.8	0.05
0.9	0.9017	134	134	268	1.5	0.9	0.05
0.9	0.9009	211	211	422	1.5	1.0	0.05
0.9	0.9001	690	690	1380	1.5	1.2	0.05
0.9	0.9000	1675	1675	3350	1.5	1.3	0.05

Target Power The desired power value entered in the procedure. Power is the probability of rejecting a false null hypothesis.
Actual Power The actual power achieved. Because N1 and N2 are discrete, this value is usually slightly larger than the target power.
N1 The number of subjects from group 1.
N2 The number of subjects from group 2.
N The total number of subjects. N = N1 + N2.
R0 The non-inferiority limit for the variance ratio.
R1 The value of the variance ratio at which the power is calculated.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design will be used to test whether the treatment variance is non-inferior to the control variance, by testing whether the variance ratio ($\sigma^2 1 / \sigma^2 2 = \sigma^2 Trt / \sigma^2 Ctrl$) is less than 1.5 (H0: $\sigma^2 1 / \sigma^2 2 \geq 1.5$ versus H1: $\sigma^2 1 / \sigma^2 2 < 1.5$). The comparison will be made using a one-sided, two-sample, variance-ratio F-test, with a Type I error rate (α) of 0.05. To detect a variance ratio of 0.8 with 90% power, the number of subjects needed will be 89 in Group 1 (treatment), and 89 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%	89	89	178	112	112	224	23	23	46
20%	134	134	268	168	168	336	34	34	68
20%	211	211	422	264	264	528	53	53	106
20%	690	690	1380	863	863	1726	173	173	346
20%	1675	1675	3350	2094	2094	4188	419	419	838

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, 112 subjects should be enrolled in Group 1, and 112 in Group 2, to obtain final group sample sizes of 89 and 89, respectively.

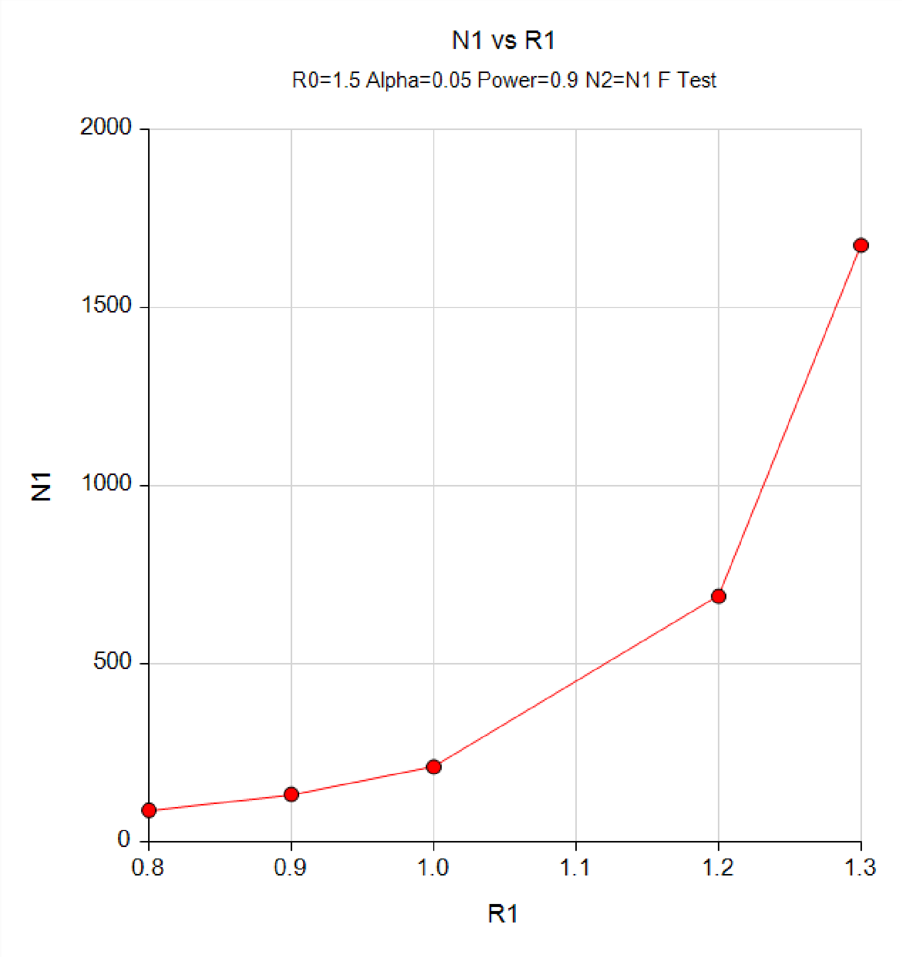
References

Johnson, N.L., Kotz, S., and Balakrishnan, N. 1995. Continuous Univariate Distributions, Volume 2, Second Edition. John Wiley & Sons. Hoboken, New Jersey.
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.
Chow, S.C., and Liu, J.P. 2014. Design and Analysis of Clinical Trials, Third Edition. John Wiley & Sons. Hoboken, New Jersey.

This report gives the sample sizes for the indicated scenarios.

Plots Section

Plots



These plots show the relationship between sample size and R1.

Example 2 – Validation using Chow et al. (2018)

The following example is shown in Chow *et al.* (2018) page 220.

Find the sample size when the non-inferiority limit is 1.21, the significance level to 0.05, the power is 0.8, and the alternative variance ratio value 0.5377778. They obtained N1 = N2 = 40.

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**
Power..**0.80**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
R0 (Non-Inferiority Variance Ratio)...............**1.21**
R1 (Actual Variance Ratio) **0.5377778**

Output

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

Numeric Results

Solve For: Sample Size
Hypotheses: H0: $\sigma^2 1/\sigma^2 2 \geq R0$ vs. H1: $\sigma^2 1/\sigma^2 2 < R0$

Power		Sample Size			Variance Ratio		
Target	Actual	N1	N2	N	Non-Inferiority R0	Actual R1	Alpha
0.8	0.8051	40	40	80	1.21	0.538	0.05

The sample sizes match Chow *et al.* (2018).