Chapter 473

Non-Inferiority Tests for the Ratio of Two Within-Subject Variances in a Parallel Design

Introduction

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

Technical Details

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

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

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

where μ_i is the treatment effect, S_{ij} is the random effect of the *j*th subject in the *i*th treatment, and e_{ijk} is the within-subject error term which is normally distributed with mean 0 and variance $V_i = \sigma_{Wi}^2$.

Unbiased estimates of these variances are given by

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

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 $N_1(M-1)$ and $N_2(M-1)$.

Testing Non-Inferiority

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

$$H_0: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \geq R0 \quad \text{versus} \quad H_1: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} < R0,$$

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

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

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 within-subject variability. A parallel-group design with replicates 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, M to 2 or 3, and the actual variance ratio values between 0.8 and 1.2. 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)**
M (Measurements Per Subject) **2 3**
R0 (Non-Inferiority Variance Ratio)................ **1.5**
R1 (Actual Variance Ratio) **0.8 0.9 1 1.1 1.2**

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
Variance Ratio: σ²w1 / σ²w2 or σ²wT / σ²wc
Hypotheses: H0: σ²wT / σ²wc ≥ R0 vs. H1: σ²wT / σ²wc < R0

Power		Sample Size			Measurements per Subject	Variance Ratio		
Target	Actual	N1	N2	N	M	Non-Inferiority R0	Actual R1	Alpha
0.9	0.9013	88	88	176	2	1.5	0.8	0.05
0.9	0.9013	44	44	88	3	1.5	0.8	0.05
0.9	0.9017	133	133	266	2	1.5	0.9	0.05
0.9	0.9036	67	67	134	3	1.5	0.9	0.05
0.9	0.9009	210	210	420	2	1.5	1.0	0.05
0.9	0.9009	105	105	210	3	1.5	1.0	0.05
0.9	0.9000	357	357	714	2	1.5	1.1	0.05
0.9	0.9007	179	179	358	3	1.5	1.1	0.05
0.9	0.9001	689	689	1378	2	1.5	1.2	0.05
0.9	0.9004	345	345	690	3	1.5	1.2	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. Each subject is measured M times.
N2 The number of subjects from group 2. Each subject is measured M times.
N The total number of subjects. N = N1 + N2.
M The number of times each subject is measured.
R0 The non-inferiority limit for the within-subject variance ratio.
R1 The value of the within-subject variance ratio at which the power is calculated.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group, repeated measurement design (with 2 measurements per subject) will be used to test whether the Group 1 (treatment) within-subject variance (σ²wT) is non-inferior to the Group 2 (control) within-subject variance (σ²wc), by testing whether the within-subject variance ratio (σ²wT / σ²wc) is less than 1.5 (H0: σ²wT / σ²wc ≥ 1.5 versus H1: σ²wT / σ²wc < 1.5). The comparison will be made using a one-sided, variance-ratio F-test (with the treatment within-subject variance in the numerator), with a Type I error rate (α) of 0.05. To detect a within-subject variance ratio (σ²wT / σ²wc) of 0.8 with 90% power, the number of subjects needed will be 88 in Group 1 (treatment), and 88 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%	88	88	176	110	110	220	22	22	44
20%	44	44	88	55	55	110	11	11	22
20%	133	133	266	167	167	334	34	34	68
20%	67	67	134	84	84	168	17	17	34
20%	210	210	420	263	263	526	53	53	106
20%	105	105	210	132	132	264	27	27	54
20%	357	357	714	447	447	894	90	90	180
20%	179	179	358	224	224	448	45	45	90
20%	689	689	1378	862	862	1724	173	173	346
20%	345	345	690	432	432	864	87	87	174

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, 110 subjects should be enrolled in Group 1, and 110 in Group 2, to obtain final group sample sizes of 88 and 88, respectively.

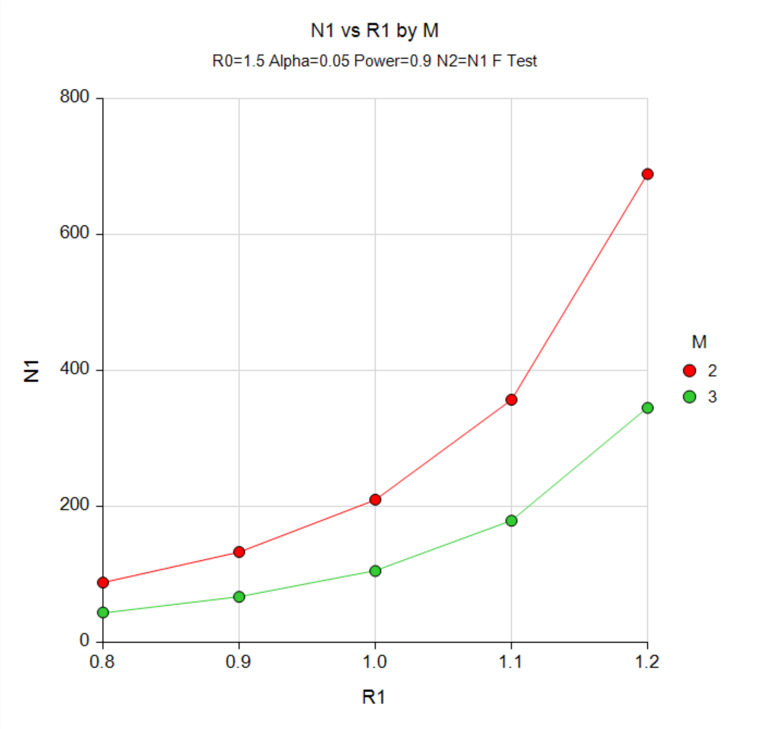
References

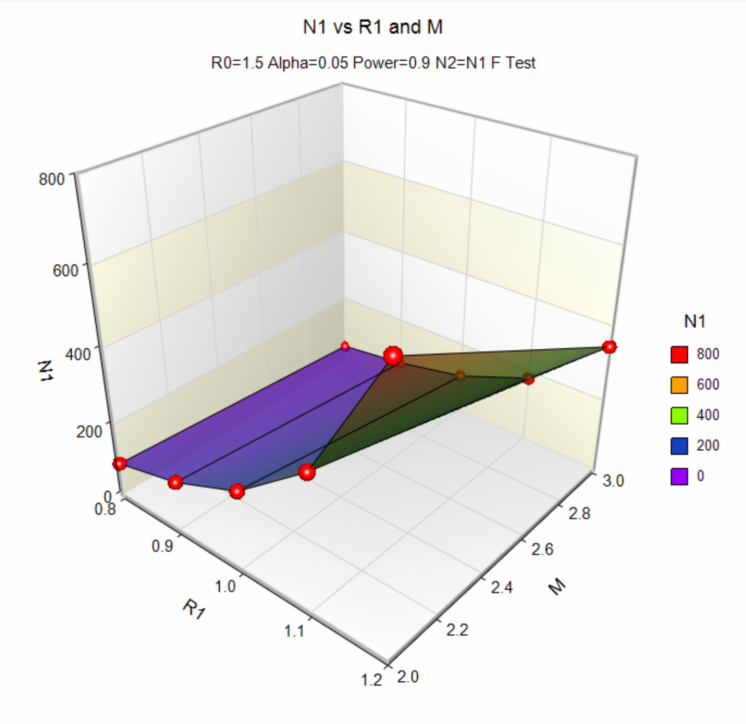
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Chow, S.C., and Liu, J.P. 2014. Design and Analysis of Clinical Trials, Third Edition. John Wiley & Sons. Hoboken, New Jersey.

This report gives the sample sizes for the indicated scenarios.

Plots Section

Plots





These plots show the relationship between sample size, R1, and M.

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

The following example is shown in Chow *et al.* (2018) page 195.

Find the sample size when the non-inferiority limit is 1.21, the significance level to 0.05, M is 3, the power is 0.8, and the alternative variance ratio value 0.44444444. They obtained N1 = N2 = 13.

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... **0.8**
Alpha.. **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **3**
R0 (Non-Inferiority Variance Ratio)................ **1.21**
R1 (Actual Variance Ratio) **0.44444444**

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
Variance Ratio: $\sigma^2 w1 / \sigma^2 w2$ or $\sigma^2 wT / \sigma^2 wC$
Hypotheses: H0: $\sigma^2 wT / \sigma^2 wC \geq R0$ vs. H1: $\sigma^2 wT / \sigma^2 wC < R0$

Power		Sample Size			Measurements	Variance Ratio		
Target	Actual	N1	N2	N	per Subject M	Non-Inferiority R0	Actual R1	Alpha
0.8	0.8072	13	13	26	3	1.21	0.444	0.05

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