Chapter 142

Non-Inferiority Tests for the Ratio of Two Within-Subject Variances in a 2×2M Replicated Cross-Over Design

Introduction

This procedure calculates power and sample size of *non-inferiority* tests of within-subject variabilities from a 2×2M replicated cross-over design. This routine deals with the case in which the statistical hypotheses are expressed in terms of the ratio of the within-subject variances.

This design is used to compare two treatments which are administered to subjects in different orders. It has two treatment sequences. Here, *M* is the number of times a particular treatment is received by a subject. For example, if *M* = 2, the design is a 2×4 cross-over. The two sequences would often be

sequence 1: R T R T

sequence 2: T R T R

It is assumed that either there is no carry-over from one measurement to the next, or there is an ample washout period between measurements.

Technical Details

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

Suppose x_{ijkl} is the response in the *i*th sequence (*i* = 1, 2), *j*th subject (*j* = 1, ..., *Ni*), *k*th treatment (*k* = T, C), and *l*th replicate (l = 1, ..., M). The mixed effect model analyzed in this procedure is

$$x_{ijkl} = \mu_k + \gamma_{ikl} + S_{ijk} + e_{ijkl}$$

where μ_k is the *k*th treatment effect, γ_{ikl} is the fixed effect of the *l*th replicate on treatment *k* in the *i*th sequence, S_{ij1} and S_{ij2} are random effects of the *ij*th subject, and e_{ijkl} is the within-subject error term which is normally distributed with mean 0 and variance $V_k = \sigma_{Wk}^2$

Unbiased estimators of these variances are found after applying an orthogonal transformation matrix *P* to the x's as follows

$$z_{ijk} = P' x_{ijk}$$

where *P* is an *m* × *m* matrix such that $P'P$ is diagonal and $\text{var}(z_{ijkl}) = \sigma_{Wk}^2$.

For example, in a 2×4 cross-over design the z's become

$$z_{ijk1} = \frac{x_{ijk1} + x_{ijk2}}{2} = \bar{x}_{ijk}.$$

and

$$z_{ijk2} = \frac{x_{ijk1} + x_{ijk2}}{\sqrt{2}} = \bar{x}_{ijk}.$$

In this case, the within-subject variances are estimated as

$$\hat{V}_T = \frac{1}{(N_1 + N_2 - 2)(M-1)} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \sum_{l=1}^{M} \left(z_{ijTl} - \bar{z}_{i.Tl}\right)^2$$

and

$$\hat{V}_C = \frac{1}{(N_1 + N_2 - 2)(M-1)} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \sum_{l=1}^{M} \left(z_{ijCl} - \bar{z}_{i.Cl}\right)^2$$

Testing Non-Inferiority

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

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

where *R0* is the non-inferiority limit.

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

Upon making the usual normality assumptions, *T* is distributed as an $F_{d,d}$ random variable where

$$d = (N_1 + N_2 - 2)(M-1).$$

Power

The power of this combination of tests is given by

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

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 2 x 4 replicated cross-over 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, M to 2, 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**
Sequence Allocation	**Equal (N1 = N2)**
M (Number of Replicates)	**2**
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
Variance Ratio: $\sigma^2_{WT} / \sigma^2_{WC}$
Hypotheses: H0: $\sigma^2_{WT} / \sigma^2_{WC} \geq R0$ vs. H1: $\sigma^2_{WT} / \sigma^2_{WC} < R0$

Power		Sequence Sample Size			Number of Replicates	Variance Ratio		
Target	Actual	N1	N2	N	M	Non-Inferiority R0	Actual R1	Alpha
0.9	0.9013	45	45	90	2	1.5	0.8	0.05
0.9	0.9036	68	68	136	2	1.5	0.9	0.05
0.9	0.9009	106	106	212	2	1.5	1.0	0.05
0.9	0.9007	180	180	360	2	1.5	1.1	0.05
0.9	0.9004	346	346	692	2	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 in sequence 1.
N2: The number of subjects in sequence 2.
N: The total number of subjects. N = N1 + N2.
M: The number of replicates. That is, it is the number of times a treatment measurement is repeated on a subject.
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 2×2M replicated cross-over design will be used to test whether the treatment within-subject variance (σ^2_{WT}) is non-inferior to the control within-subject variance (σ^2_{WC}), by testing whether the within-subject variance ratio ($\sigma^2_{WT} / \sigma^2_{WC}$) is less than 1.5 (H0: $\sigma^2_{WT} / \sigma^2_{WC} \geq 1.5$ versus H1: $\sigma^2_{WT} / \sigma^2_{WC} < 1.5$). Each subject will alternate treatments (T and C), with an assumed wash-out period between measurements to avoid carry-over. With 2 replicate pairs, each subject will be measured 4 times. For those in the Sequence 1 group, the first treatment will be C, and the sequence is [C T C T]. For those in the Sequence 2 group, the first treatment will be T, and the sequence is [T C T C]. 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 ($\sigma^2_{WT} / \sigma^2_{WC}$) of 0.8 with 90% power, the number of subjects needed will be 45 in Group/Sequence 1, and 45 in Group/Sequence 2.

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%	45	45	90	57	57	114	12	12	24
20%	68	68	136	85	85	170	17	17	34
20%	106	106	212	133	133	266	27	27	54
20%	180	180	360	225	225	450	45	45	90
20%	346	346	692	433	433	866	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, 57 subjects should be enrolled in Group 1, and 57 in Group 2, to obtain final group sample sizes of 45 and 45, respectively.

References

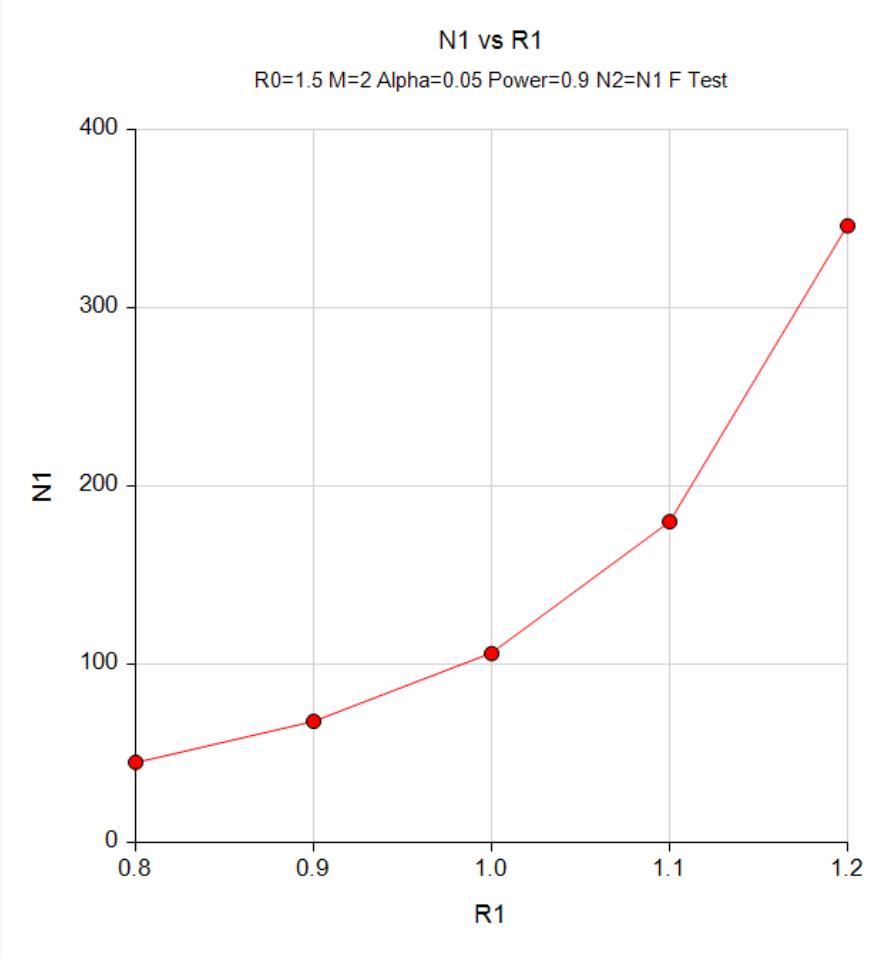
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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 and R1.

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

The following example of finding the sample size for a 2x4 cross-over design is shown in Chow *et al.* (2018) pages 199 - 200.

Find the sample size when the non-inferiority limit is 1.21, the significance level to 0.05, M is 2, the power is 0.8, and the alternative variance ratio value 0.4444. They obtained N1 = N2 = 14.

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**
Sequence Allocation	**Equal (N1 = N2)**
M (Number of Replicates)	**2**
R0 (Non-Inferiority Variance Ratio)	**1.21**
R1 (Actual Variance Ratio)	**0.444**

Output

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

Numeric Results

Solve For: Sample Size
Variance Ratio: $\sigma^2_{WT} / \sigma^2_{WC}$
Hypotheses: H0: $\sigma^2_{WT} / \sigma^2_{WC} \geq R0$ vs. H1: $\sigma^2_{WT} / \sigma^2_{WC} < R0$

Power		Sequence Sample Size			Number of Replicates	Variance Ratio		
Target	Actual	N1	N2	N	M	Non-Inferiority R0	Actual R1	Alpha
0.8	0.8079	14	14	28	2	1.21	0.444	0.05

The sequence sample sizes are 14 and match the results of Chow et al. (2018).