Chapter 302

Non-Inferiority Tests for Two Between-Subject Variances in a 2×2M Replicated Cross-Over Design

Introduction

This procedure calculates power and sample size of *non-inferiority* tests of between-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 between-subject variances.

This design is used to compare two treatments which are administered to subjects in different orders. The design 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 replicated cross-over. The two sequences might be

sequence 1: C T C T

sequence 2: T C T C

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), pages 213 - 216.

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 $\text{var}(z_{ijkl}) = \sigma_{Wk}^2$.

Let $N_s = N_1 + N_2 - 2$. In a 2×4 cross-over design the z's become

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

and

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

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

$$s_{WT}^2 = \frac{1}{N_S(M-1)} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \sum_{l=1}^{M} \left(z_{ijTl} - \bar{z}_{i\cdot Tl}\right)^2$$

and

$$s_{WC}^2 = \frac{1}{N_S(M-1)} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \sum_{l=1}^{M} \left(z_{ijCl} - \bar{z}_{i\cdot Cl}\right)^2$$

Similarly, the between-subject variances are estimated as

$$s_{BT}^2 = \frac{1}{N_S} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \left(\bar{x}_{ijT\cdot} - \bar{x}_{i\cdot T\cdot}\right)^2$$

and

$$s_{BC}^2 = \frac{1}{N_S} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \left(\bar{x}_{ijC\cdot} - \bar{x}_{i\cdot C\cdot}\right)^2$$

where

$$\bar{x}_{i\cdot k\cdot} = \frac{1}{N_i} \sum_{j=1}^{N_i} \bar{x}_{ijk\cdot}$$

Now, since $E(s_{BK}^2) = \sigma_{BK}^2 + \sigma_{WK}^2/M$, estimators for the between-subject variance are given by

$$\hat{\sigma}_{BK}^2 = s_{BK}^2 - \hat{\sigma}_{WK}^2/M$$

The sample between-subject covariance is calculated using

$$s_{BTC}^2 = \frac{1}{N_S} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \left(\bar{x}_{ijT\cdot} - \bar{x}_{i\cdot T\cdot}\right)\left(\bar{x}_{ijC\cdot} - \bar{x}_{i\cdot C\cdot}\right)$$

Using this value, the sample between-subject correlation is easily calculated.

Testing Variance Non-Inferiority

The following statistical hypotheses are used to test for between-subject variance non-inferiority.

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

where *R0* is the non-inferiority limit.

Let $\eta = \sigma_{BT}^2 - R0\sigma_{BC}^2$ be the parameter of interest. The test statistic is $\hat{\eta} = \hat{\sigma}_{BT}^2 - R0\hat{\sigma}_{BC}^2$.

Non-Inferiority Test

For the non-inferiority test, compute the limit $\hat{\eta}_U$ using

$$\hat{\eta}_U = \hat{\eta} + \sqrt{\Delta_U}$$

Reject the null hypothesis if $\hat{\eta}_U < 0$.

The Δ is given by

$$\Delta_U = h(1-\alpha, N_s - 1)\lambda_1^2 + h(\alpha, N_s - 1)\lambda_2^2 + h\big(1-\alpha, N_s(M-1)\big)\frac{\hat{\sigma}_{WT}^4}{M^2} + h\big(\alpha, N_s(M-1)\big)\frac{\hat{\sigma}_{WC}^4}{M^2}$$

where

$$h(A,B) = \left(1 - \frac{B}{\chi_{A,B}^2}\right)^2$$

$$\lambda_i^2 = \left(\frac{s_{BT}^2 - s_{BC}^2 \pm \sqrt{(s_{BT}^2 + s_{BC}^2)^2 - 4(R0)s_{BTC}^4}}{2}\right) \text{ for } i = 1,2$$

and $\chi_{A,B}^2$ is the upper quantile of the chi-square distribution with *B* degrees of freedom.

Power

Non-Inferiority Test

The power of the non-inferiority test is given by

$$\text{Power} = \Phi\left(z_\alpha - \frac{(R_1 - R_0)\sigma_{BC}^2}{\sqrt{\sigma^{*2}/N_s}}\right)$$

where

$$R_1 = \frac{\sigma_{BT}^2}{\sigma_{BC}^2}$$

$$\sigma_{BT}^2 = R_1\sigma_{BC}^2$$

$$\sigma^{*2} = 2\left[\left(\sigma_{BT}^2 + \frac{\sigma_{WT}^2}{M}\right)^2 + R_0^2\left(\sigma_{BC}^2 + \frac{\sigma_{WC}^2}{M}\right)^2 + \frac{\sigma_{WT}^4}{M^2(M-1)} + \frac{R_0^2\sigma_{WC}^4}{M^2(M-1)} - 2R_0R_1\sigma_{BC}^4\rho^2\right]$$

where *R1* is the value of the variance ratio stated by the alternative hypothesis and $\Phi(x)$ is the standard normal CDF.

A simple binary search algorithm can be applied to the 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 between-subject variability. A 2 x 4 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 0.9 and 1.3. They also set $\sigma^2_{BC} = 0.4$, $\sigma^2_{WT} = 0.2$, $\sigma^2_{WC} = 0.3$, and $\rho = 0.75$. They want to investigate the range of required sample size values assuming that the two sequence 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)	**0.9 1 1.1 1.2 1.3**
σ^2_{BC} (Control Variance)	**0.4**
σ^2_{WT} (Treatment Variance)	**0.2**
σ^2_{WC} (Control Variance)	**0.3**
ρ (Treatment, Control Correlation)	**0.75**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Hypotheses: H0: $\sigma^2_{BT}/\sigma^2_{BC} \geq R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} < R0$

Power		Sequence Sample Size			Number of Replicates	Between-Subject Variance Ratio			Within-Subject Variance		Between-Subject (Treatment, Control) Correlation	
Target	Actual	N1	N2	N	M	Non-Inferiority R0	Actual R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.9	0.9011	107	107	214	2	1.5	0.9	0.4	0.2	0.3	0.75	0.05
0.9	0.9010	156	156	312	2	1.5	1.0	0.4	0.2	0.3	0.75	0.05
0.9	0.9009	248	248	496	2	1.5	1.1	0.4	0.2	0.3	0.75	0.05
0.9	0.9005	450	450	900	2	1.5	1.2	0.4	0.2	0.3	0.75	0.05
0.9	0.9001	1038	1038	2076	2	1.5	1.3	0.4	0.2	0.3	0.75	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 between-subject variance ratio.
R1	The value of the between-subject variance ratio at which the power is calculated.
σ^2_{BC}	The between-subject variance of measurements in the control group.
σ^2_{WT}	The within-subject variance of measurements in the treatment group.
σ^2_{WC}	The within-subject variance of measurements in the control group.
ρ	The between-subject correlation of the average subject treatment-group measurements versus the average subject control-group measurements.
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 between-subject variance of the treatment (σ^2_{BT}) is non-inferior to the between-subject variance of the control (σ^2_{BC}) by testing the between-subject variance ratio (σ^2_{BT} / σ^2_{BC}) against the non-inferiority ratio 1.5 (H0: σ^2_{BT} / $\sigma^2_{BC} \geq 1.5$ versus H1: σ^2_{BT} / $\sigma^2_{BC} < 1.5$). 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-difference test (treatment minus control) as described in Chow, Shao, Wang, and Lokhnygina (2018), with a Type I error rate (α) of 0.05. For the control group, the between-subject variance (σ^2_{BC}) is assumed to be 0.4, and the within-subject variance is assumed to be 0.3. The within-subject variance of the treatment group is assumed to be 0.2. The between-subject correlation between the average treatment measurement per subject and the average control measurement per subject is assumed to be 0.75. To detect a between-subject variance ratio (σ^2_{BT} / σ^2_{BC}) of 0.9 with 90% power, the number of subjects needed will be 107 in Group/Sequence 1, and 107 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%	107	107	214	134	134	268	27	27	54
20%	156	156	312	195	195	390	39	39	78
20%	248	248	496	310	310	620	62	62	124
20%	450	450	900	563	563	1126	113	113	226
20%	1038	1038	2076	1298	1298	2596	260	260	520

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, 134 subjects should be enrolled in Group 1, and 134 in Group 2, to obtain final group sample sizes of 107 and 107, respectively.

References

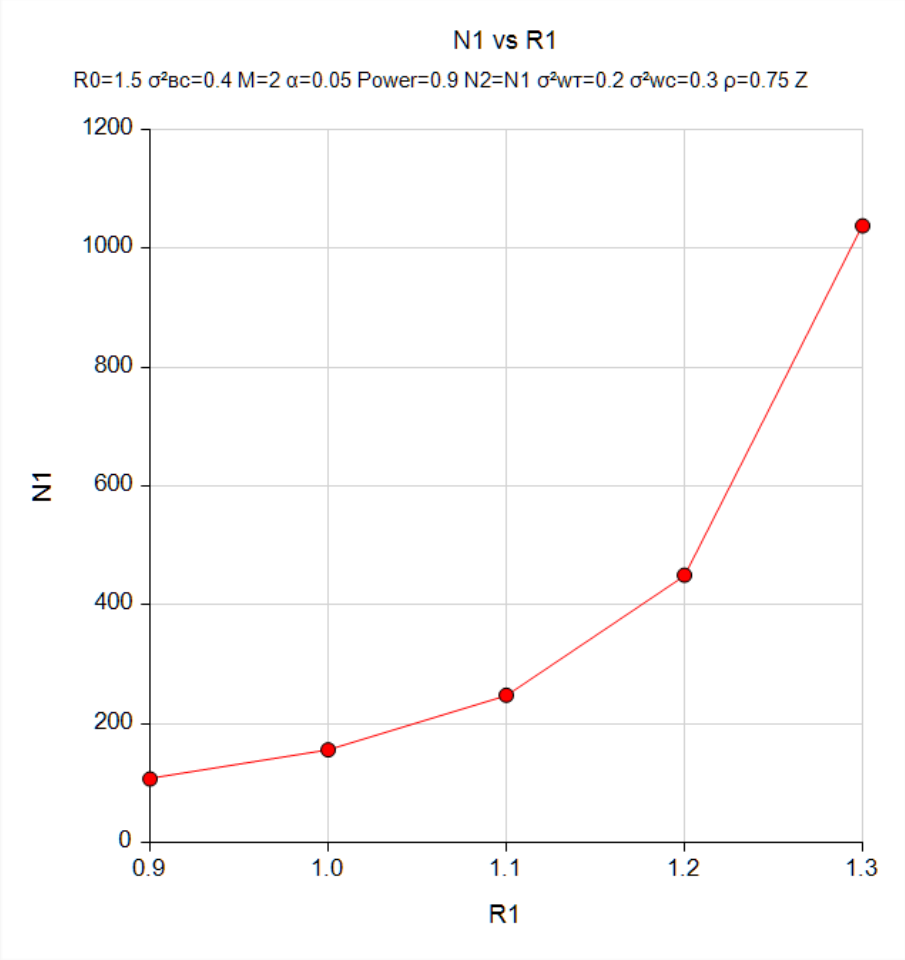
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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



This plot shows the relationship between sample size and R1.

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

We will use an example from Chow *et al.* (2018) page 217 to validate this procedure.

In this example, R0 = 1.21, significance level = 0.05, power = 0.80, M = 2, σ_{BT} = 0.3, σ_{BC} = 0.4, σ_{WT} = 0.2, σ_{WC} = 0.3, and ρ =0.75. From these values, we find that R1 = 0.5625. The resulting sample size, after some rounding, is found to be 34 per sequence. (There is a typo in the book which puts the value at 29. This is an obvious error since Ns – 2 is found to be 66.

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	**0.80**
Alpha	**0.05**
Sequence Allocation	**Equal (N1 = N2)**
M (Number of Replicates)	**2**
R0 (Non-Inferiority Variance Ratio)	**1.21**
R1 (Actual Variance Ratio)	**0.5625**
σ^2_{BC} (Control Variance)	**0.16**
σ^2_{WT} (Treatment Variance)	**0.04**
σ^2_{WC} (Control Variance)	**0.09**
ρ (Treatment, Control Correlation)	**0.75**

Output

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

Numeric Results

Solve For: Sample Size
Hypotheses: H0: $\sigma^2_{BT}/\sigma^2_{BC} \geq R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} < R0$

Power		Sequence Sample Size			Number of Replicates	Between-Subject Variance Ratio		Between-Subject Variance	Within-Subject Variance		Between-Subject (Treatment, Control) Correlation	
Target	Actual	N1	N2	N	M	Non-Inferiority R0	Actual R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.8	0.8097	35	35	70	2	1.21	0.563	0.16	0.04	0.09	0.75	0.05

The per-group sample size of 35 is one more than the value of 34 which is given in the reference. Their number yields a power that is slightly less than the desired 0.8, so **PASS** has increased the sequence sizes by one to 35.