Chapter 306

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

Introduction

This procedure calculates power and sample size of non-inferiority tests of total variabilities (between + within) 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 total 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 227 - 230.

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

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

and

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

Similarly, the between-subject variances are estimated as

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

and

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

where

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

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

$$\hat{\sigma}_{TK}^2 = s_{BK}^2 + \frac{(M-1)}{M}\hat{\sigma}_{WK}^2$$

The sample between-subject covariance is calculated using

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

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

Testing Variance Non-Inferiority

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

$$H_0\colon \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \geq R0 \quad \text{versus} \quad H_1\colon \frac{\sigma_{TT}^2}{\sigma_{TC}^2} < R0,$$

where *R0* is the non-inferiority limit.

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

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

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

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

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

where

$$R_1 = \frac{\sigma_{TT}^2}{\sigma_{TC}^2}$$

$$\sigma_{TT}^2 = R_1\sigma_{TC}^2$$

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

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 total 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 0.8 and 1.3. They also set σ^2_{TC} = 0.4, σ^2_{WT} = 0.2, σ^2_{WC} = 0.3, and ρ = 0.7. 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) **0.8 0.9 1 1.1 1.2 1.3**
σ^2_{TC} (Control Variance).................................. **0.4**
σ^2_{WT} (Treatment Variance) **0.2**
σ^2_{WC} (Control Variance)................................ **0.3**
ρ (Treatment, Control Correlation)................. **0.7**

Output

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

Numeric Reports

Numeric Results

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

Power		Sequence Sample Size			Number of Replicates	Total Variance: Ratio		Total Variance	Within-Subject Variance		Between-Subject (Treatment, Control) Correlation	
Target	Actual	N1	N2	N	M	Non-Inferiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.9	0.9065	27	27	54	2	1.5	0.8	0.4	0.2	0.3	0.7	0.05
0.9	0.9036	38	38	76	2	1.5	0.9	0.4	0.2	0.3	0.7	0.05
0.9	0.9042	58	58	116	2	1.5	1.0	0.4	0.2	0.3	0.7	0.05
0.9	0.9022	96	96	192	2	1.5	1.1	0.4	0.2	0.3	0.7	0.05
0.9	0.9013	183	183	366	2	1.5	1.2	0.4	0.2	0.3	0.7	0.05
0.9	0.9004	444	444	888	2	1.5	1.3	0.4	0.2	0.3	0.7	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 total variance ratio.
R1	The value of the total variance ratio at which the power is calculated.
σ^2_{TC}	The total variance of measurements in the control group. Note that $\sigma^2_{TC} = \sigma^2_{BC} + \sigma^2_{WC}$.
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 total variance of the treatment (σ^2_{TT}) is non-inferior to the total variance of the control (σ^2_{TC}) by testing the total variance ratio (σ^2_{TT} / σ^2_{TC}) against the non-inferiority ratio 1.5 (H0: σ^2_{TT} / σ^2_{TC} ≥ 1.5 versus H1: σ^2_{TT} / σ^2_{TC} < 1.5). 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 total variance (σ^2_{TC}) 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 0.7. To detect a total variance ratio (σ^2_{TT} / σ^2_{TC}) of 0.8 with 90% power, the number of subjects needed will be 27 in Group/Sequence 1, and 27 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%	27	27	54	34	34	68	7	7	14
20%	38	38	76	48	48	96	10	10	20
20%	58	58	116	73	73	146	15	15	30
20%	96	96	192	120	120	240	24	24	48
20%	183	183	366	229	229	458	46	46	92
20%	444	444	888	555	555	1110	111	111	222

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, 34 subjects should be enrolled in Group 1, and 34 in Group 2, to obtain final group sample sizes of 27 and 27, respectively.

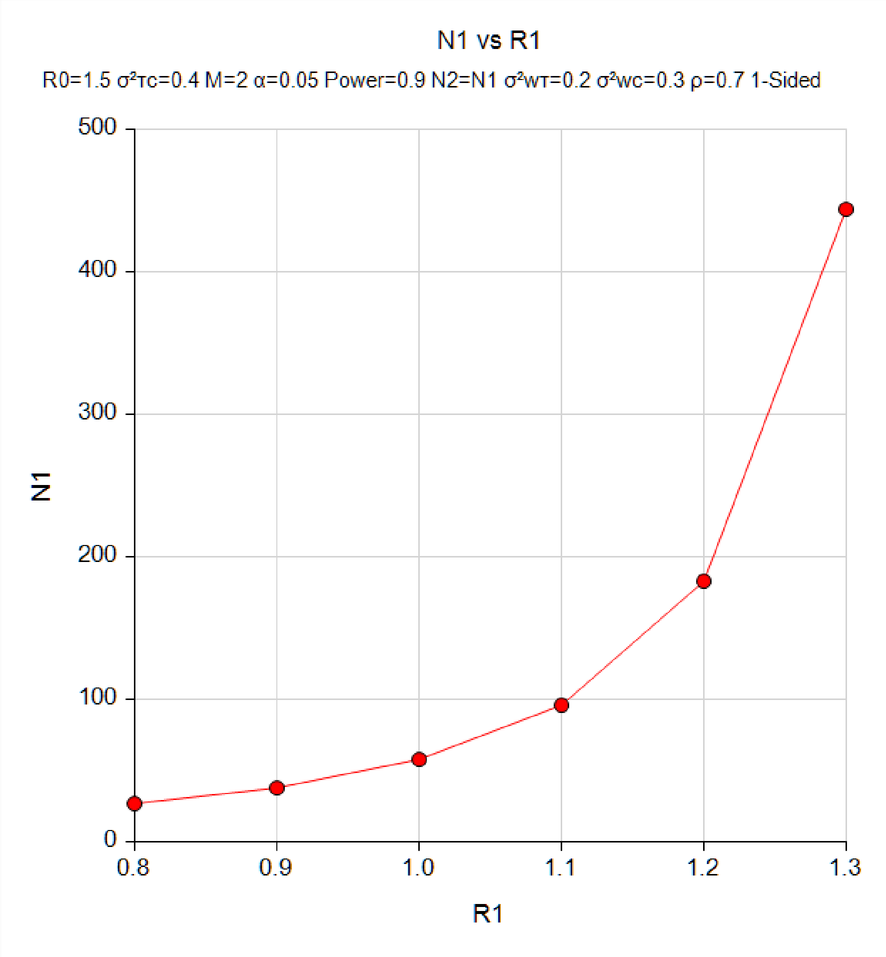
References

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 Hand Calculations

We could not find an example in the literature, so we will present hand calculations to validate this procedure. (Note that example 9.4.4.3 in Chow *et al.* (2018) page 230 contains many mistakes, so we could not use it.)

Set N1 = 200, R0 = 1.2, significance level = 0.05, M = 2, and R1 = 1.0. Also, σ^2_{TC} = 0.4, σ^2_{WT} = 0.2, σ^2_{WC} = 0.3, and ρ = 0.7. Compute the power for the non-inferiority test.

The calculations proceed as follows.

$$\sigma^2_{TT} = R1(\sigma^2_{TC}) = 1.0(0.4) = 0.4$$

$$\sigma^2_{BT} = \sigma^2_{TT} - \sigma^2_{WT} = 0.4 - 0.2 = 0.2$$

$$\sigma^2_{BC} = \sigma^2_{TC} - \sigma^2_{WC} = 0.4 - 0.3 = 0.1$$

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

$$\sigma^{*2} = 2\left[\left(0.2 + \frac{0.2}{2}\right)^2 + 1.44\left(0.1 + \frac{0.3}{2}\right)^2 + \frac{0.04}{4} + \frac{1.44(0.09)}{4} - 2(1.2)(0.2)(0.1)(0.49)\right]$$

$$\sigma^{*2} = 2[0.09 + 0.09 + 0.01 + 0.0324 - 0.02352] = 0.39776$$

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

$$\text{Power} = \Phi\left(-1.6448536 - \frac{(1-1.2)0.4}{\sqrt{0.39776/398}}\right)$$

$$\text{Power} = \Phi(-1.6448536 + 2.53058523)$$

$$\text{Power} = \Phi(0.88573163) = 0.8121189$$

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**
Alpha.. **0.05**
Sequence Allocation .... **Equal (N1 = N2)**
Sample Size Per Sequence **200**
M (Number of Replicates) **2**
R0 (Non-Inferiority Variance Ratio)................ **1.2**
R1 (Actual Variance Ratio) **1**
σ^2_{TC} (Control Variance)................................. **0.4**
σ^2_{WT} (Treatment Variance) **0.2**
σ^2_{WC} (Control Variance)................................ **0.3**
ρ (Treatment, Control Correlation) **0.7**

Output

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

Numeric Results

Solve For: Power
Hypotheses: H0: $\sigma^2_{TT}/\sigma^2_{TC} \geq$ R0 vs. H1: $\sigma^2_{TT}/\sigma^2_{TC} <$ R0

	Sequence Sample Size				Total Variance			Within-Subject Variance			
					Ratio						
Power	N1	N2	N	Number of Replicates M	Non-Inferiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Between-Subject (Treatment, Control) Correlation ρ	Alpha
0.8121	200	200	400	2	1.2	1	0.4	0.2	0.3	0.7	0.05

The power matches the hand-calculated result.