Chapter 314

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

Introduction

This procedure calculates power and sample size of non-inferiority tests of total variabilities (between + within) from a 2×2 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. The two sequences are

sequence 1: C T

sequence 2: 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 224 - 227.

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

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

where μ_k is the *k*th treatment effect, γ_{ik} is the interaction between sequence *i* and treatment *k*, S_{ijT} and S_{ijC} are random effects of the *ij*th subject, and e_{ijk} is the within-subject error term which is normally distributed with mean 0 and variance $V_k = \sigma_{Wk}^2$.

Let $N_s = N_1 + N_2 - 2$. The total variances ($\sigma_{Tk}^2 = \sigma_{Bk}^2 + \sigma_{Wk}^2,\ k = T, C$) are estimated by

$$\hat{\sigma}_{TK}^2 = s_{Tk}^2 = \frac{1}{N_S}\sum_{i=1}^{2}\sum_{j=1}^{N_i}\left(\bar{x}_{ijk} - \bar{x}_{i.k}\right)^2$$

where

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

The sample between-subject covariance is calculated using

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

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.

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

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

$$\Delta_U = h(\alpha, N_s)\lambda_1^2 + h(1-\alpha, N_s)\lambda_2^2$$

where

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

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

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

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

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

$$\sigma^{*2} = 2[\sigma_{TT}^4 + R_0^2\sigma_{TC}^4 - 2R_0\sigma_{BT}^2\sigma_{BC}^2\rho^2]$$

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 2 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, and the actual variance ratio values between 0.8 and 1.3. They also set $\sigma^2_{TC} = 0.8$, $\sigma^2_{WT} = 0.2$, $\sigma^2_{WC} = 0.3$, and $\rho = 0.7$. 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)**
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)	**0.8**
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			Total Variance Ratio			Within-Subject Variance		Between-Subject (Treatment, Control) Correlation	
Target	Actual	N1	N2	N	Non-Inferiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.9	0.9020	43	43	86	1.5	0.8	0.8	0.2	0.3	0.7	0.05
0.9	0.9018	60	60	120	1.5	0.9	0.8	0.2	0.3	0.7	0.05
0.9	0.9008	89	89	178	1.5	1.0	0.8	0.2	0.3	0.7	0.05
0.9	0.9011	145	145	290	1.5	1.1	0.8	0.2	0.3	0.7	0.05
0.9	0.9009	270	270	540	1.5	1.2	0.8	0.2	0.3	0.7	0.05
0.9	0.9004	639	639	1278	1.5	1.3	0.8	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.
R0	The non-inferiority limit for the total variance ratio.
R1	The value of the total variance ratio at which the power is calculated. R1 = σ^2_{TT} / σ^2_{TC}.
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 treatment versus control measurements.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A 2×2 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 whether the total variance ratio (σ^2_{TT} / σ^2_{TC}) is less than the non-inferiority ratio 1.5 (H0: σ^2_{TT} / $\sigma^2_{TC} \geq 1.5$ versus H1: σ^2_{TT} / $\sigma^2_{TC} < 1.5$). Each subject will alternate treatments (T and C), with an assumed wash-out period between measurements to avoid carry-over. For those in the Sequence 1 group, the first treatment will be C, and the sequence is [C T]. For those in the Sequence 2 group, the first treatment will be T, and the sequence is [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 0.8, 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 treatment and control measurements 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 43 in Group/Sequence 1, and 43 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%	43	43	86	54	54	108	11	11	22
20%	60	60	120	75	75	150	15	15	30
20%	89	89	178	112	112	224	23	23	46
20%	145	145	290	182	182	364	37	37	74
20%	270	270	540	338	338	676	68	68	136
20%	639	639	1278	799	799	1598	160	160	320

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, 54 subjects should be enrolled in Group 1, and 54 in Group 2, to obtain final group sample sizes of 43 and 43, respectively.

References

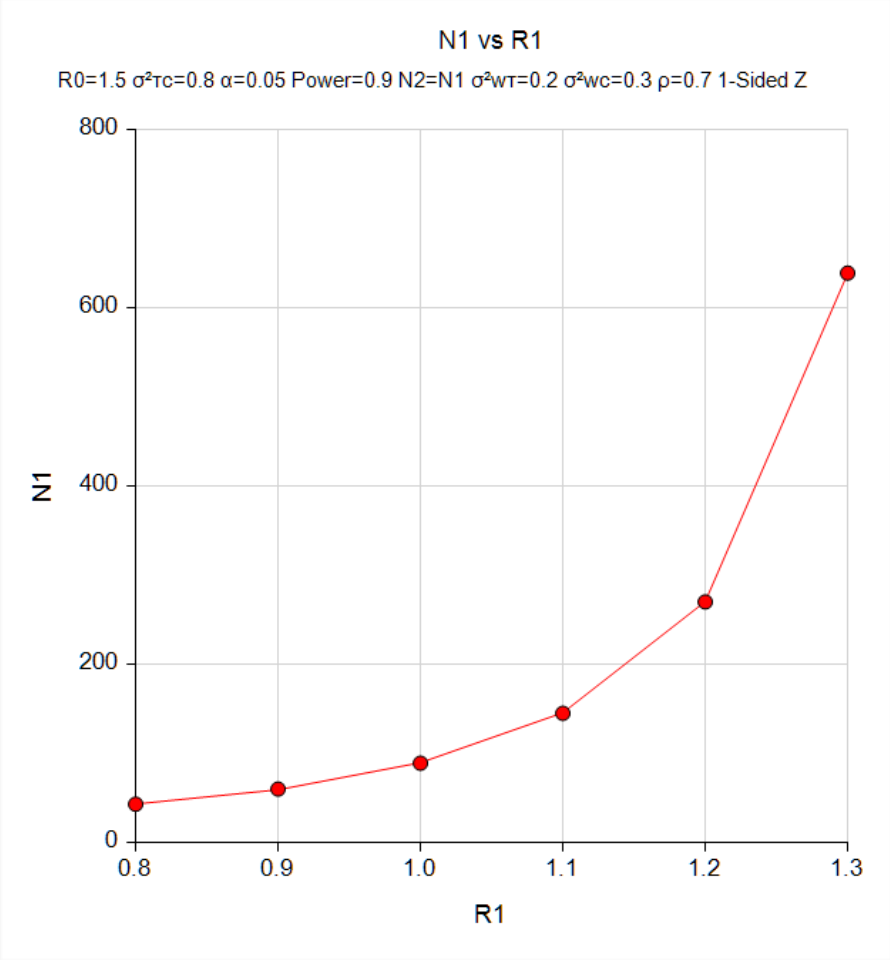
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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)

Chow *et al.* (2018) page 227 contains an example that we will use to validate this procedure.

Set power = 0.8, R0 = 1.21, significance level = 0.05, and R1 = 0.52. Also, $\sigma^2_{TC} = 0.25$, $\sigma^2_{WT} = 0.04$, $\sigma^2_{WC} = 0.09$, and $\rho = 1.0$. The sample size per sequence is computed to be 17.

Note that there is a typo in the book. The variance estimate of 0.147 is changed to 0.153 in the formula for n_s. This error is not enough to change the final result.

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)**
R0 (Non-Inferiority Variance Ratio)	**1.21**
R1 (Actual Variance Ratio)	**0.52**
σ^2_{TC} (Control Variance)	**0.25**
σ^2_{WT} (Treatment Variance)	**0.04**
σ^2_{WC} (Control Variance)	**0.09**
ρ (Treatment, Control Correlation)	**1**

Output

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

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			Total Variance Ratio		Total Variance	Within-Subject Variance		Between-Subject (Treatment, Control)	
Target	Actual	N1	N2	N	Non-Inferiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Correlation ρ	Alpha
0.8	0.8157	17	17	34	1.21	0.52	0.25	0.04	0.09	1	0.05

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