Chapter 315

Superiority by a Margin Tests for Two Total Variances in a 2×2 Cross-Over Design

Introduction

This procedure calculates power and sample size of *superiority by a margin* 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 Superiority

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 superiority limit.

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

Superiority by a Margin Test

For the superiority 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

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

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

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

Power

Superiority by a Margin Test

The power of the superiority 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 superior to the standard drug in terms of the total variability. A 2 x 2 cross-over design will be used to test the superiority.

Company researchers set the superior limit to 0.8, the significance level to 0.05, the power to 0.90, and the actual variance ratio values between 0.4 and 0.7. 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 (Superiority Variance Ratio)	**0.8**
R1 (Actual Variance Ratio)	**0.4 0.5 0.6 0.7**
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)	
Target	Actual	N1	N2	N	Superiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Correlation ρ	Alpha
0.9	0.9008	40	40	80	0.8	0.4	0.8	0.2	0.3	0.7	0.05
0.9	0.9034	75	75	150	0.8	0.5	0.8	0.2	0.3	0.7	0.05
0.9	0.9009	179	179	358	0.8	0.6	0.8	0.2	0.3	0.7	0.05
0.9	0.9000	780	780	1560	0.8	0.7	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 superiority 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 superior 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 superiority ratio 0.8 (H0: σ^2_{TT} / $\sigma^2_{TC} \geq 0.8$ versus H1: σ^2_{TT} / $\sigma^2_{TC} < 0.8$). 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 0.4 with 90% power, the number of subjects needed will be 40 in Group/Sequence 1, and 40 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%	40	40	80	50	50	100	10	10	20
20%	75	75	150	94	94	188	19	19	38
20%	179	179	358	224	224	448	45	45	90
20%	780	780	1560	975	975	1950	195	195	390

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, 50 subjects should be enrolled in Group 1, and 50 in Group 2, to obtain final group sample sizes of 40 and 40, respectively.

References

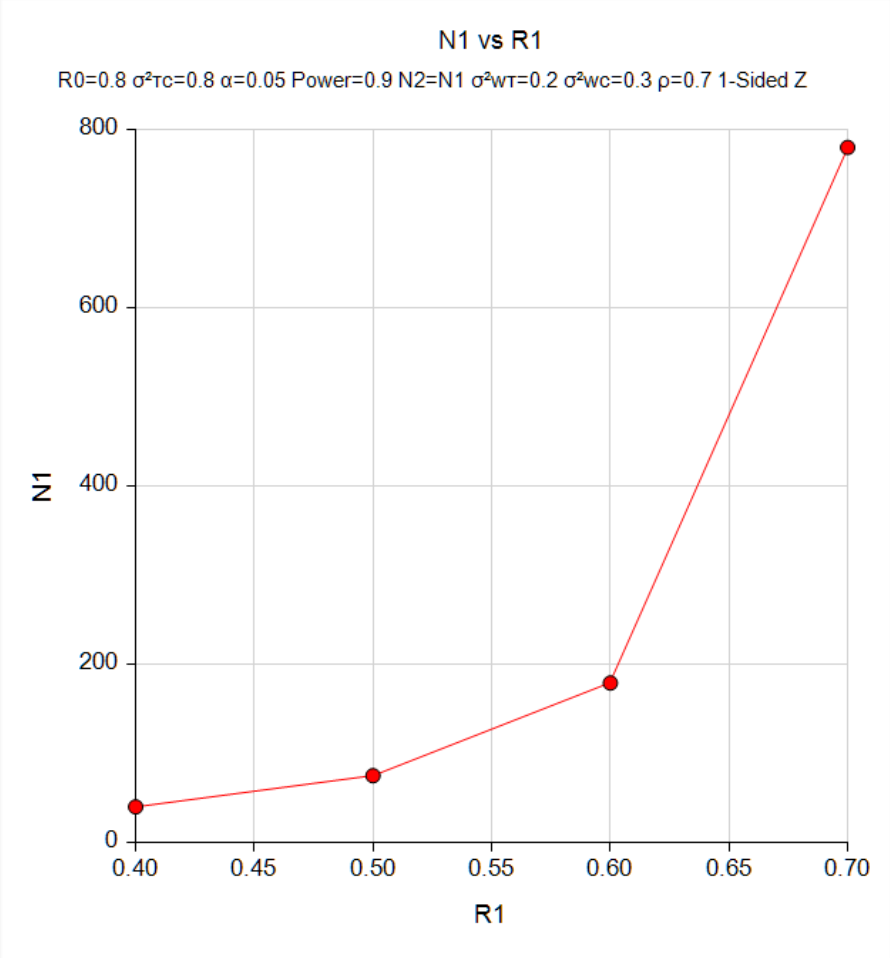
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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 another PASS Procedure

We previously validated the **Non-Unity Null Tests for Two Total Variances in a 2×2 Cross-Over Design** procedure which can be used to run this example. Hence, we will run an example through that procedure and use it to validate this procedure.

In the **Non-Unity Null Tests for Two Total Variances in a 2×2 Cross-Over Design procedure,** set the superiority ratio to 0.8, the significance level to 0.05, the power to 0.80, and the actual variance ratio to 0.5. Also set $\sigma^2_{TC} = 0.8$, $\sigma^2_{WT} = 0.2$, $\sigma^2_{WC} = 0.3$, and $\rho = 0.7$. The sample size is computed as 54 per sequence for the lower, one-sided case.

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 (Superiority Variance Ratio)	**0.8**
R1 (Actual Variance Ratio)	**0.5**
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 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	Superiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.8	0.8018	54	54	108	0.8	0.5	0.8	0.2	0.3	0.7	0.05

The sample size of 54 per sequence matches the expected result.