Chapter 301

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

Introduction

This procedure calculates power and sample size of tests of between-subject variabilities from a 2×2M replicated cross-over design for the case when the ratio assumed by the null hypothesis is not necessarily equal to one. 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

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

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 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

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

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

Testing Variance Inequality with a Non-Unity Null

The following three sets of statistical hypotheses are used to test for between-subject variance inequality with a non-unity null

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

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

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

where *R0* is the variance ratio assumed by the null hypothesis.

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

Two-Sided Test

For the two-sided test, compute two limits, $\hat{\eta}_L$ and $\hat{\eta}_U$, using

$$\hat{\eta}_L = \hat{\eta} - \sqrt{\Delta_L}$$

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

Reject the null hypothesis if $\hat{\eta}_L > 0$ is or $\hat{\eta}_U < 0$.

The Δs are given by

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

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

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.

One-Sided Test

For the lower, one-sided 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_U is given by

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

Power

Two-Sided Test

The power of the two-sided test is given by

$$\text{Power} = 1 - \Phi\left(z_{1-\frac{\alpha}{2}} - \frac{(R_1 - R_0)\sigma_{BC}^2}{\sqrt{\sigma^{*2}/N_s}}\right) + \Phi\left(z_{\alpha/2} - \frac{(R_1 - R_0)\sigma_{BC}^2}{\sqrt{\sigma^{*2}/N_s}}\right)$$

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.

One-Sided Test

The power of the lower, one-sided test, $H_0: \frac{\sigma_{BT}^2}{\sigma_{BC}^2} \geq R0$ versus $H_1: \frac{\sigma_{BT}^2}{\sigma_{BC}^2} < R0$, is given by

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

The power of the upper, one-sided test, $H_0: \frac{\sigma_{BT}^2}{\sigma_{BC}^2} \leq R0$ versus $H_1: \frac{\sigma_{BT}^2}{\sigma_{BC}^2} > R0$, is given by

$$\text{Power} = 1 - \Phi\left(z_{1-\alpha} - \frac{(R_1 - R_0)\sigma_{BC}^2}{\sqrt{\sigma^{*2}/N_s}}\right)$$

Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to compare it to the standard drug in terms of the between-subject variability. A 2 x 4 cross-over design will be used to test the inequality using a two-sided test.

Company researchers set the variance ratio under the null hypothesis to 0.8, the significance level to 0.05, the power to 0.90, M to 2, and the actual variance ratio values between 0.5 and 1.1. They also set σ^2_{BC} = 0.4, σ^2_{WT} = 0.2, σ^2_{WC} = 0.3, and ρ =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**
Alternative Hypothesis	**Two-Sided (H1: $\sigma^2_{BT}/\sigma^2_{BC} \neq$ R0)**
Power	**0.90**
Alpha	**0.05**
Sequence Allocation	**Equal (N1 = N2)**
M (Number of Replicates)	**2**
R0 (H0 Variance Ratio)	**0.8**
R1 (Actual Variance Ratio)	**0.5 0.6 0.7 0.9 1 1.1**
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: $\sigma^2_{BT}/\sigma^2_{BC}$ = 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	H0 (Null) R0	Actual R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.9	0.9013	174	174	348	2	0.8	0.5	0.4	0.2	0.3	0.75	0.05
0.9	0.9001	407	407	814	2	0.8	0.6	0.4	0.2	0.3	0.75	0.05
0.9	0.9000	1719	1719	3438	2	0.8	0.7	0.4	0.2	0.3	0.75	0.05
0.9	0.9001	1972	1972	3944	2	0.8	0.9	0.4	0.2	0.3	0.75	0.05
0.9	0.9000	533	533	1066	2	0.8	1.0	0.4	0.2	0.3	0.75	0.05
0.9	0.9008	258	258	516	2	0.8	1.1	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 between-subject variance ratio used to define the null hypothesis, H0.
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 ratio (σ^2_{BT} / σ^2_{BC} = σ^2Between,Treatment / σ^2Between,Control) is different from 0.8 (H0: σ^2_{BT} / σ^2_{BC} = 0.8 versus H1: σ^2_{BT} / σ^2_{BC} ≠ 0.8). 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 two-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 0.5 with 90% power, the number of subjects needed will be 174 in Group/Sequence 1, and 174 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%	174	174	348	218	218	436	44	44	88
20%	407	407	814	509	509	1018	102	102	204
20%	1719	1719	3438	2149	2149	4298	430	430	860
20%	1972	1972	3944	2465	2465	4930	493	493	986
20%	533	533	1066	667	667	1334	134	134	268
20%	258	258	516	323	323	646	65	65	130

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, 218 subjects should be enrolled in Group 1, and 218 in Group 2, to obtain final group sample sizes of 174 and 174, respectively.

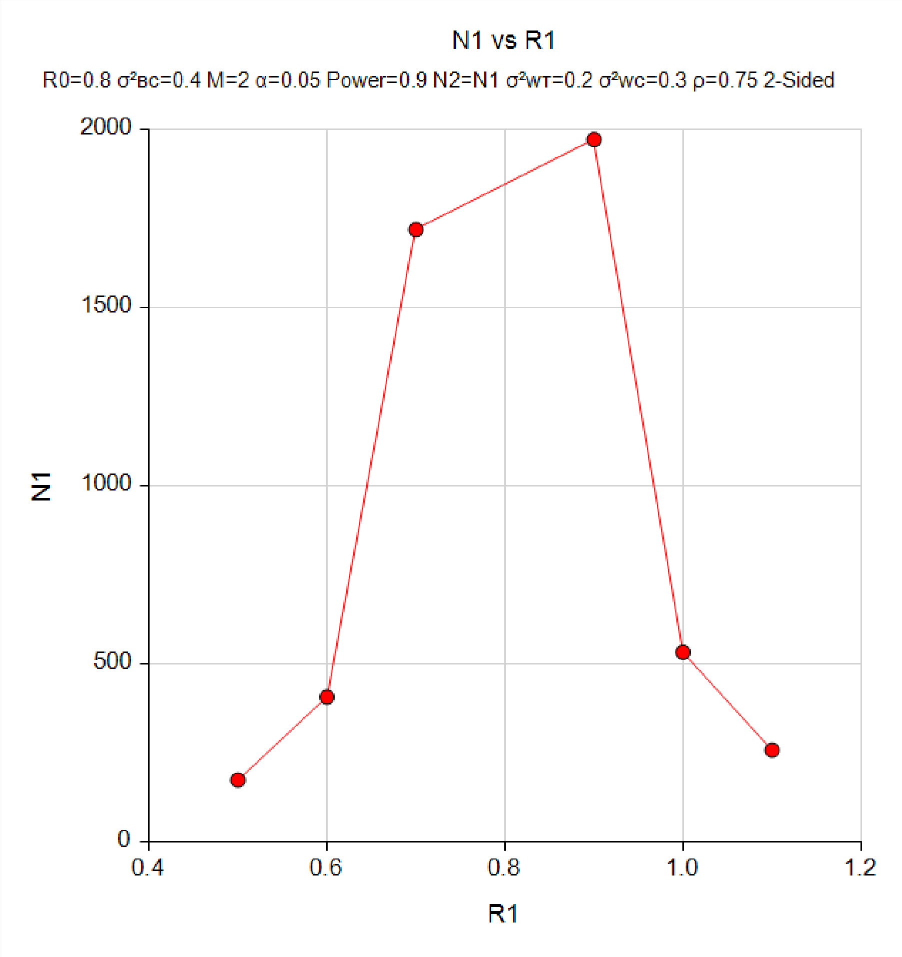
References

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 and Liu (2014)

We will use an example from Chow and Liu (2014) page 517 to validate this procedure.

In this example, R0 = 1, 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 is found to be 66 per sequence.

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**
Alternative Hypothesis	**Two-Sided (H1: $\sigma^2_{BT}/\sigma^2_{BC}$ ≠ R0)**
Power	**0.80**
Alpha	**0.05**
Sequence Allocation	**Equal (N1 = N2)**
M (Number of Replicates)	**2**
R0 (H0 Variance Ratio)	**1**
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: $\sigma^2_{BT}/\sigma^2_{BC}$ = R0 vs. H1: $\sigma^2_{BT}/\sigma^2_{BC}$ ≠ R0

Power		Sequence Sample Size				Between-Subject Variance			Within-Subject Variance			
						Ratio						
Target	Actual	N1	N2	N	Number of Replicates M	H0 (Null) R0	Actual R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Between-Subject (Treatment, Control) Correlation ρ	Alpha
0.8	0.8022	66	66	132	2	1	0.563	0.16	0.04	0.09	0.75	0.05

The sample sizes match Chow and Liu (2014).