Chapter 141

Non-Unity Null Tests for the Ratio of Within-Subject Variances in a 2×2M Replicated Cross-Over Design

Introduction

This procedure calculates power and sample size of inequality tests of within-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 within-subject variances.

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

sequence 1: R T R T

sequence 2: T R T R

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).

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

For example, in a 2×4 cross-over design the z's become

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

and

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

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

$$\hat{V}_T = \frac{1}{(N_1 + N_2 - 2)(M-1)} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \sum_{l=1}^{M} \left(z_{ijTl} - \bar{z}_{i.Tl}\right)^2$$

and

$$\hat{V}_C = \frac{1}{(N_1 + N_2 - 2)(M-1)} \sum_{i=1}^{2} \sum_{j=1}^{N_i} \sum_{l=1}^{M} \left(z_{ijCl} - \bar{z}_{i.Cl}\right)^2$$

Testing Variance Inequality with a Non-Unity Null

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

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

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

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

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

The corresponding test statistics are $T = (\hat{V}_T/\hat{V}_C)/R0$. Upon making the usual normality assumptions, *T* is distributed as an $F_{d,d}$ random variable where

$$d = (N_1 + N_2 - 2)(M-1).$$

Power

The corresponding powers of these three tests are given by

$$\text{Power} = \text{P}\left(F < \frac{R0}{R1} F_{\alpha,d,d}\right)$$

$$\text{Power} = 1 - \text{P}\left(F < \frac{R0}{R1} F_{1-\alpha,d,d}\right)$$

$$\text{Power} = \text{P}\left(F < \frac{R0}{R1} F_{\alpha/2,d,d}\right) + 1 - \text{P}\left(F < \frac{R0}{R1} F_{1-\alpha/2,d,d}\right)$$

where *F* is the common F distribution with the indicated degrees of freedom, α is the significance level, and *R1* is the value of the variance ratio stated by the alternative hypothesis. Lower quantiles of F are used in the equation.

A simple binary search algorithm can be applied to this 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 compare it to the standard drug in terms of the within-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 0.75, the significance level to 0.05, the power to 0.90, M to 2, and the actual variance ratio values between 0.5 and 1.2. They want to investigate the range of required sample size values assuming that the two group 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: $\sigma^2_{WT}/\sigma^2_{WC} \neq R0$)**
Power	**0.90**
Alpha	**0.05**
Sequence Allocation	**Equal (N1 = N2)**
M (Number of Replicates)	**2**
R0 (H0 Variance Ratio)	**0.75**
R1 (Actual Variance Ratio)	**0.5 0.6 0.9 1 1.1 1.2**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Variance Ratio: $\sigma^2_{WT} / \sigma^2_{WC}$
Hypotheses: H0: $\sigma^2_{WT}/\sigma^2_{WC} = R0$ vs. H1: $\sigma^2_{WT}/\sigma^2_{WC} \neq R0$

Power		Sequence Sample Size			Number of Replicates	Variance Ratio		
Target	Actual	N1	N2	N	M	H0 (Null) R0	Actual R1	Alpha
0.9	0.9015	130	130	260	2	0.75	0.5	0.05
0.9	0.9003	424	424	848	2	0.75	0.6	0.05
0.9	0.9001	634	634	1268	2	0.75	0.9	0.05
0.9	0.9006	256	256	512	2	0.75	1.0	0.05
0.9	0.9005	145	145	290	2	0.75	1.1	0.05
0.9	0.9011	97	97	194	2	0.75	1.2	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 within-subject variance ratio used to define the null hypothesis, H0.
R1: The value of the within-subject variance ratio ($\sigma^2_{WT}/\sigma^2_{WC}$) at which the power is calculated.
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 within-subject variance ratio ($\sigma^2_{WT} / \sigma^2_{WC}$ = $\sigma^2_{Within,Treatment} / \sigma^2_{Within,Control}$) is different from 0.75 (H0: $\sigma^2_{WT} / \sigma^2_{WC} = 0.75$ versus H1: $\sigma^2_{WT} / \sigma^2_{WC} \neq 0.75$). 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-ratio F-test (with the treatment within-subject variance in the numerator), with a Type I error rate (α) of 0.05. To detect a within-subject variance ratio ($\sigma^2_{WT} / \sigma^2_{WC}$) of 0.5 with 90% power, the number of subjects needed will be 130 in Group/Sequence 1, and 130 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%	130	130	260	163	163	326	33	33	66
20%	424	424	848	530	530	1060	106	106	212
20%	634	634	1268	793	793	1586	159	159	318
20%	256	256	512	320	320	640	64	64	128
20%	145	145	290	182	182	364	37	37	74
20%	97	97	194	122	122	244	25	25	50

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, 163 subjects should be enrolled in Group 1, and 163 in Group 2, to obtain final group sample sizes of 130 and 130, respectively.

References

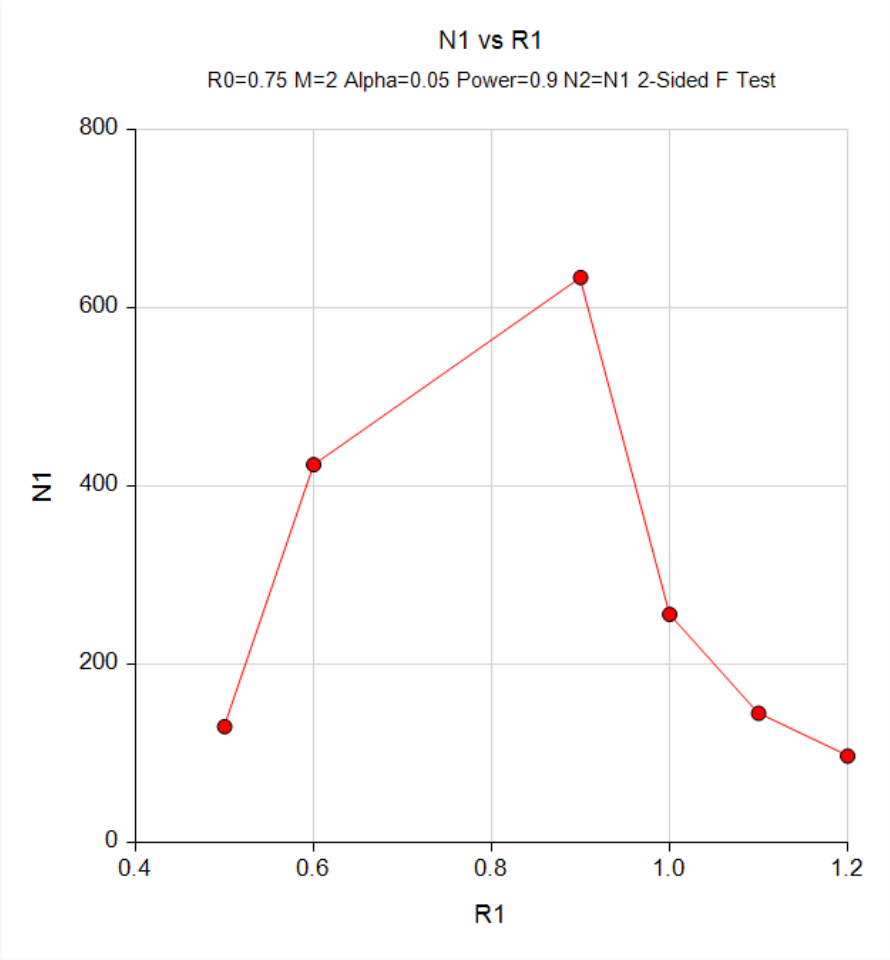
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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 509 to validate this procedure.

In this example, the significance level to 0.05, M is 2, the power is 0.80, and the actual variance ratio is 0.3/0.45 or about 0.667. The resulting sample size is found to be 98 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: $\sigma^2_{WT}/\sigma^2_{WC} \neq R0$)**
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)	**0.667**

Output

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

Numeric Results

Solve For: Sample Size
Variance Ratio: $\sigma^2_{WT} / \sigma^2_{WC}$
Hypotheses: H0: $\sigma^2_{WT}/\sigma^2_{WC} = R0$ vs. H1: $\sigma^2_{WT}/\sigma^2_{WC} \neq R0$

Power		Sequence Sample Size			Number of Replicates	Variance Ratio		
Target	Actual	N1	N2	N	M	H0 (Null) R0	Actual R1	Alpha
0.8	0.8032	98	98	196	2	1	0.667	0.05

The sample sizes match Chow and Liu (2014).