Chapter 479

Non-Unity Null Tests for the Ratio of Within-Subject Variances in a Parallel Design

Introduction

This procedure calculates power and sample size of inequality tests of within-subject variabilities from a two-group, parallel design with replicates (repeated measurements) 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.

Technical Details

This procedure uses the formulation given in Chow, Shao, Wang, and Lokhnygina (2018).

Suppose x_{ijk} is the response of the i^{th} treatment (*i* = 1,2), j^{th} subject (*j* = 1, ..., *Ni*), and k^{th} replicate (*k* = 1, ..., M). The model analyzed in this procedure is

$$x_{ijk} = \mu_i + S_{ij} + e_{ijk}$$

where μ_i is the treatment effect, S_{ij} is the random effect of the j^{th} subject in the i^{th} treatment, and e_{ijk} is the within-subject error term which is normally distributed with mean 0 and variance $V_i = \sigma_{Wi}^2$.

Unbiased estimates of these variances are given by

$$\hat{V}_i = \frac{1}{N_i(M-1)} \sum_{j=1}^{N_i} \sum_{k=1}^{M} \left(x_{ijk} - \bar{x}_{ij.}\right)^2$$

A common test statistic to compare variabilities in the two groups is $T = \hat{V}_1/\hat{V}_2$. Under the usual normality assumptions, *T* is distributed as an *F* distribution with degrees of freedom $N_1(M-1)$ and $N_2(M-1)$.

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

$$H_0: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \geq R0 \quad \text{versus} \quad H_1: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} < R0,$$

$$H_0: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \leq R0 \quad \text{versus} \quad H_1: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} > R0,$$

$$H_0: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} = R0 \quad \text{versus} \quad H_1: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \neq R0,$$

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

The corresponding test statistic is $T = (\hat{V}_1/\hat{V}_2)/R0$.

Power

The corresponding powers of these three tests are given by

$$\text{Power} = \Pr\left(F < \frac{R0}{R1}\, F_{\alpha, N_1(M-1), N_2(M-1)}\right)$$

$$\text{Power} = 1 - \Pr\left(F < \frac{R0}{R1}\, F_{1-\alpha, N_1(M-1), N_2(M-1)}\right)$$

$$\text{Power} = \Pr\left(F < \frac{R0}{R1}\, F_{\alpha/2, N_1(M-1), N_2(M-1)}\right) + 1 - \Pr\left(F < \frac{R0}{R1}\, F_{1-\alpha/2, N_1(M-1), N_2(M-1)}\right)$$

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 parallel-group design with replicates 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 or 3, 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: $\sigma^2 w_1$ / $\sigma^2 w_2$ ≠ R0)**
Power.. **0.9**
Alpha... **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **2 3**
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
Groups: 1 = Treatment, 2 = Control
Variance Ratio: $\sigma^2 w1 / \sigma^2 w2$ or $\sigma^2 wT / \sigma^2 wC$
Hypotheses: H0: $\sigma^2 wT / \sigma^2 wC = R0$ vs. H1: $\sigma^2 wT / \sigma^2 wC \neq R0$

Power		Sample Size			Measurements per Subject	Variance Ratio		
Target	Actual	N1	N2	N	M	H0 (Null) R0	Actual R1	Alpha
0.9	0.9004	257	257	514	2	0.75	0.5	0.05
0.9	0.9015	129	129	258	3	0.75	0.5	0.05
0.9	0.9003	846	846	1692	2	0.75	0.6	0.05
0.9	0.9003	423	423	846	3	0.75	0.6	0.05
0.9	0.9001	1266	1266	2532	2	0.75	0.9	0.05
0.9	0.9001	633	633	1266	3	0.75	0.9	0.05
0.9	0.9001	509	509	1018	2	0.75	1.0	0.05
0.9	0.9006	255	255	510	3	0.75	1.0	0.05
0.9	0.9005	288	288	576	2	0.75	1.1	0.05
0.9	0.9005	144	144	288	3	0.75	1.1	0.05
0.9	0.9011	192	192	384	2	0.75	1.2	0.05
0.9	0.9011	96	96	192	3	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 from group 1. Each subject is measured M times.
N2 The number of subjects from group 2. Each subject is measured M times.
N The total number of subjects. N = N1 + N2.
M The number of times each subject is measured.
R0 The within-subject variance ratio used to define the null hypothesis, H0.
R1 The value of the within-subject variance ratio at which the power is calculated.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group, repeated measurement design (with 2 measurements per subject) will be used to test whether the Group 1 (treatment) within-subject variance ($\sigma^2 wT$) is different from the Group 2 (control) within-subject variance ($\sigma^2 wC$), by testing whether the within-subject variance ratio ($\sigma^2 wT / \sigma^2 wC$) is different from 0.75 (H0: $\sigma^2 wT / \sigma^2 wC = 0.75$ versus H1: $\sigma^2 wT / \sigma^2 wC \neq 0.75$). 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 257 in Group 1 (treatment), and 257 in Group 2 (control).

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%	257	257	514	322	322	644	65	65	130
20%	129	129	258	162	162	324	33	33	66
20%	846	846	1692	1058	1058	2116	212	212	424
20%	423	423	846	529	529	1058	106	106	212
20%	1266	1266	2532	1583	1583	3166	317	317	634
20%	633	633	1266	792	792	1584	159	159	318
20%	509	509	1018	637	637	1274	128	128	256
20%	255	255	510	319	319	638	64	64	128
20%	288	288	576	360	360	720	72	72	144
20%	144	144	288	180	180	360	36	36	72
20%	192	192	384	240	240	480	48	48	96
20%	96	96	192	120	120	240	24	24	48

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, 322 subjects should be enrolled in Group 1, and 322 in Group 2, to obtain final group sample sizes of 257 and 257, respectively.

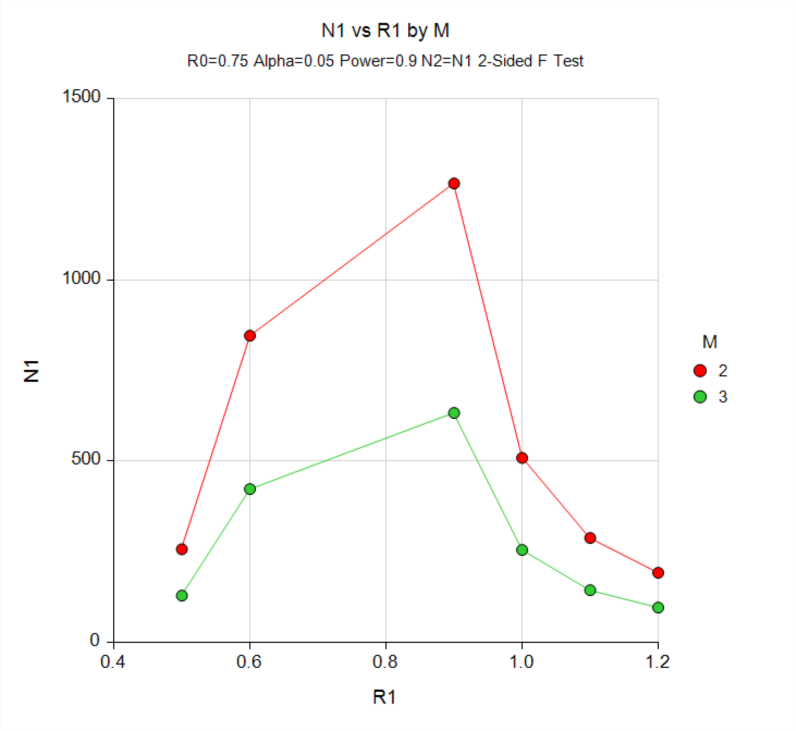
References

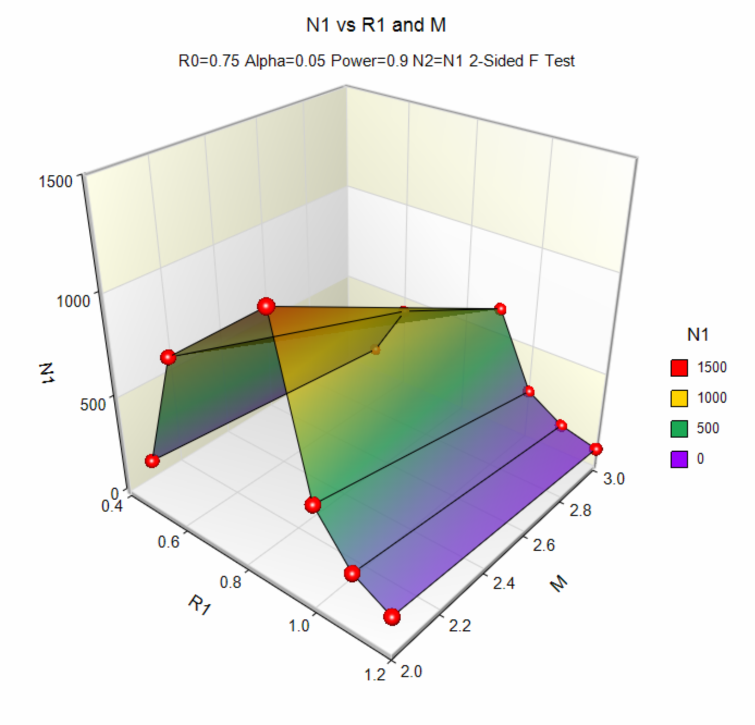
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Chow, S.C., and Liu, J.P. 2014. Design and Analysis of Clinical Trials, Third Edition. John Wiley & Sons. Hoboken, New Jersey.

This report gives the sample sizes for the indicated scenarios.

Plots Section

Plots





These plots show the relationship between sample size, R1, and M.

Example 2 – Validation using Chow et al. (2018)

The following example is shown in Chow *et al.* (2018) page 195.

Find the sample size when R0 is 1.21, the significance level to 0.05, M is 3, the power is 0.8, and R1 is 0.44444444. They obtained N1 = N2 = 13. Their example is for a non-inferiority test.

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	**One-Sided (H1: $\sigma^2 w_1/\sigma^2 w_2$ < R0)**
Power	**0.80**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
M (Measurements Per Subject)	**3**
R0 (H0 Variance Ratio)	**1.21**
R1 (Actual Variance Ratio)	**0.44444444**

Output

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

Numeric Results

Solve For: Sample Size
Groups: 1 = Treatment, 2 = Control
Variance Ratio: $\sigma^2 w1 / \sigma^2 w2$ or $\sigma^2 wT / \sigma^2 wC$
Hypotheses: H0: $\sigma^2 wT / \sigma^2 wC \geq R0$ vs. H1: $\sigma^2 wT / \sigma^2 wC < R0$

Power		Sample Size			Measurements per Subject	Variance Ratio		
Target	Actual	N1	N2	N	M	H0 (Null) R0	Actual R1	Alpha
0.8	0.8072	13	13	26	3	1.21	0.444	0.05

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