Chapter 466

Equivalence Tests for the Ratio of Two Within-Subject Variances in a Parallel Design

Introduction

This procedure calculates power and sample size of *equivalence* tests of within-subject variabilities from a two-group, parallel design with replicates.

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 Equivalence

The following hypotheses are usually used to test for equivalence

$$H_0\colon \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \geq RU \ \text{ or } \ \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \leq RL \quad \text{versus} \quad H_1\colon RL < \frac{\sigma_{W1}^2}{\sigma_{W2}^2} < RU,$$

where RL and RU are the equivalence limits.

These hypotheses can be tested using the two one-sided hypotheses

$$H_{01}: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \geq RU \quad \text{versus} \quad H_{11}: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} < RU$$

and

$$H_{02}: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} \leq RL \quad \text{versus} \quad H_{12}: \frac{\sigma_{W1}^2}{\sigma_{W2}^2} > RL$$

The corresponding test statistics are $T_1 = RU\ (\hat{V}_1/\hat{V}_2)$ and $T_2 = RL\ (\hat{V}_1/\hat{V}_2)$.

Power

The power of this combination of tests is given by

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

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 show that it is equivalent to the standard drug with respect to the within-subject variance. A parallel-group design with replicates (repeated measures) will be used to test the equivalence of the two drugs.

Company researchers set the upper limit of equivalence to 1.5, the lower limit to 1/1.5, the significance level to 0.05, the power to 0.90, M to 2 or 3, and the actual variance ratio values between 0.8 and 1.3. 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**
Power	**0.9**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
M (Measurements Per Subject)	**2 3**
RU (Upper Equivalence Limit)	**1.5**
RL (Lower Equivalence Limit)	**1/RU**
R1 (Actual Variance Ratio)	**0.8 0.9 1 1.1 1.2 1.3**

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: $σ^2w1 / σ^2w2$ or $σ^2wT / σ^2wC$
Hypotheses: H0: $σ^2wT / σ^2wC ≤ RL$ or $σ^2wT / σ^2wC ≥ RU$ vs. H1: $RL < σ^2wT / σ^2wC < RU$

Power		Sample Size			Measurements	Variance Ratio: Equivalence Limits		Variance Ratio	
Target	Actual	N1	N2	N	per Subject M	Lower RL	Upper RU	Actual R1	Alpha
0.9	0.9002	1032	1032	2064	2	0.667	1.5	0.8	0.05
0.9	0.9002	516	516	1032	3	0.667	1.5	0.8	0.05
0.9	0.9001	382	382	764	2	0.667	1.5	0.9	0.05
0.9	0.9001	191	191	382	3	0.667	1.5	0.9	0.05
0.9	0.9009	265	265	530	2	0.667	1.5	1.0	0.05
0.9	0.9022	133	133	266	3	0.667	1.5	1.0	0.05
0.9	0.9004	359	359	718	2	0.667	1.5	1.1	0.05
0.9	0.9012	180	180	360	3	0.667	1.5	1.1	0.05
0.9	0.9001	689	689	1378	2	0.667	1.5	1.2	0.05
0.9	0.9004	345	345	690	3	0.667	1.5	1.2	0.05
0.9	0.9000	1674	1674	3348	2	0.667	1.5	1.3	0.05
0.9	0.9000	837	837	1674	3	0.667	1.5	1.3	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.
RL The lower equivalence (similarity) limit for the within-subject variance ratio.
RU The upper equivalence limit for the within-subject variance ratio.
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 ($σ^2wT$) is equivalent to the Group 2 (control) within-subject variance ($σ^2wC$), by testing whether the within-subject variance ratio ($σ^2wT / σ^2wC$) is between 0.667 and 1.5 (H0: $σ^2wT / σ^2wC ≤ 0.667$ or $σ^2wT / σ^2wC ≥ 1.5$ versus H1: $0.667 < σ^2wT / σ^2wC < 1.5$). The comparison will be made using two one-sided, variance-ratio F-tests (with the treatment within-subject variance in the numerator), with an overall Type I error rate (α) of 0.05. To detect a within-subject variance ratio ($σ^2wT / σ^2wC$) of 0.8 with 90% power, the number of subjects needed will be 1032 in Group 1 (treatment), and 1032 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%	1032	1032	2064	1290	1290	2580	258	258	516
20%	516	516	1032	645	645	1290	129	129	258
20%	382	382	764	478	478	956	96	96	192
20%	191	191	382	239	239	478	48	48	96
20%	265	265	530	332	332	664	67	67	134
20%	133	133	266	167	167	334	34	34	68
20%	359	359	718	449	449	898	90	90	180
20%	180	180	360	225	225	450	45	45	90
20%	689	689	1378	862	862	1724	173	173	346
20%	345	345	690	432	432	864	87	87	174
20%	1674	1674	3348	2093	2093	4186	419	419	838
20%	837	837	1674	1047	1047	2094	210	210	420

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, 1290 subjects should be enrolled in Group 1, and 1290 in Group 2, to obtain final group sample sizes of 1032 and 1032, respectively.

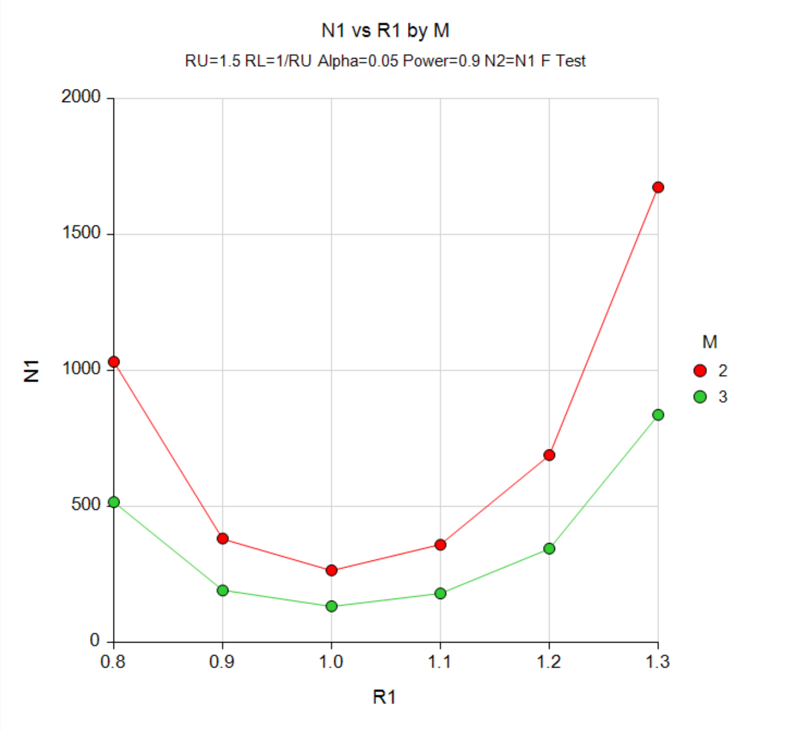
References

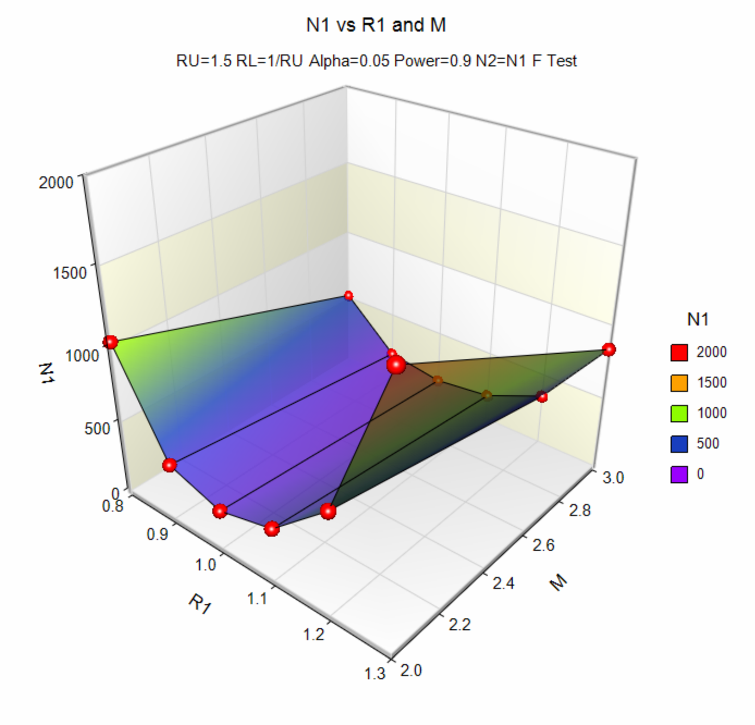
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Chow, S.C. 2014. Biosimilars Design and Analysis of Follow-on Biologics, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Chow, S.C., 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 Hand Calculations

We could not find an example in the literature, so we will present hand calculations to validate this procedure.

Set N1 to 265, the upper limit of equivalence to 1.5, the lower limit to 1/1.5, the significance level to 0.05, M to 2, and the actual variance ratio values 1.0. Compute the power.

The calculations proceed as follows.

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

$$= \text{P}\left(0.666667/1 \left(F_{0.95,265,265}\right) < F < 1.5/1 \left(F_{0.05,265,265}\right)\right)$$

$$= \text{P}\big(0.666667(1.22439660) < F < 1.5(0.81672883)\big)$$

$$= \text{P}(0.81626440 < F < 1.22509325)$$

$$= 0.95047403 - 0.049525978$$

$$= 0.90094805$$

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	**Power**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**265**
M (Measurements Per Subject)	**2**
RU (Upper Equivalence Limit)	**1.5**
RL (Lower Equivalence Limit)	**1/RU**
R1 (Actual Variance Ratio)	**1.0**

Output

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

Numeric Results

Solve For: Power
Groups: 1 = Treatment, 2 = Control
Variance Ratio: σ^2w1 / σ^2w2 or $\sigma^2w_T / \sigma^2w_C$
Hypotheses: H0: $\sigma^2w_T / \sigma^2w_C \leq RL$ or $\sigma^2w_T / \sigma^2w_C \geq RU$ vs. H1: $RL < \sigma^2w_T / \sigma^2w_C < RU$

	Sample Size				Variance Ratio: Equivalence Limits			
Power	N1	N2	N	Measurements per Subject M	Lower RL	Upper RU	Actual R1	Alpha
0.9009	265	265	530	2	0.667	1.5	1	0.05

The power matches and our hand calculations.