Chapter 317

Non-Unity Null Tests for Two Between Variances in a Replicated Design

Introduction

This procedure calculates power and sample size of tests of the between-subject variance (between + within) from a parallel (two-group) design with replicates (repeated measures) for the case when the ratio assumed by the null hypothesis is not necessarily one. This routine deals with the case in which the statistical hypotheses are expressed in terms of the ratio of the between-subject variances.

A parallel design is used to compare two treatment groups by comparing subjects receiving each treatment. In this replicated design, each subject is measured *M* times where *M* is at least two. To be clear, each subject receives only on treatment, but is measured repeatedly.

Replicated parallel designs such as this are popular because they allow the assessment of total variances, between-subject variances, and within-subject variances.

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 209 - 212.

Suppose x_{ijk} is the response of the *i*th treatment (*i* = T, C), *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

$$\hat{\sigma}_{Wi}^2 = s_{Wi}^2 = \frac{1}{N_i(M-1)} \sum_{j=1}^{N_i} \sum_{k=1}^{M} \left(x_{ijk} - \bar{x}_{ij.}\right)^2 \ , i = T, C$$

where

$$\bar{x}_{ij.} = \frac{1}{M} \sum_{k=1}^{M} x_{ijk}$$

Define

$$s_{Bi}^2 = \frac{1}{N_i - 1} \sum_{j=1}^{N_i} \left(\bar{x}_{ij.} - \bar{x}_{i..}\right)^2$$

where

$$\bar{x}_{i..} = \frac{1}{N_i} \sum_{j=1}^{N_i} \bar{x}_{ij.}$$

Now, estimators for the between-subject variance are given by

$$\hat{\sigma}_{Bi}^2 = s_{Bi}^2 - \frac{1}{M} \hat{\sigma}_{Wi}^2$$

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

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

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

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

where *R0* is the variance ratio assumed by the null hypothesis (usually, one).

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

$$\Delta_L = h\left(\frac{\alpha}{2}, N_T - 1\right) s_{BT}^4 + h\left(1 - \frac{\alpha}{2}, N_C - 1\right) R_0^2 s_{BC}^4 + h\left(1 - \frac{\alpha}{2}, N_T(M-1)\right)\left[\frac{s_{WT}^2}{M}\right]^2 + h\left(\frac{\alpha}{2}, N_C(M-1)\right)\left[\frac{R_0 s_{WC}^2}{M}\right]^2$$

$$\Delta_U = h\left(1 - \frac{\alpha}{2}, N_T - 1\right) s_{BT}^4 + h\left(\frac{\alpha}{2}, N_C - 1\right) R_0^2 s_{BC}^4 + h\left(\frac{\alpha}{2}, N_T(M-1)\right)\left[\frac{s_{WT}^2}{M}\right]^2 + h\left(1 - \frac{\alpha}{2}, N_C(M-1)\right)\left[\frac{R_0 s_{WC}^2}{M}\right]^2$$

where

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

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

$$\Delta_U = h(1-\alpha, N_T - 1) s_{BT}^4 + h(\alpha, N_C - 1) R_0^2 s_{BC}^4 + h\big(\alpha, N_T(M-1)\big)\left[\frac{s_{WT}^2}{M}\right]^2 + h\big(1-\alpha, N_C(M-1)\big)\left[\frac{R_0 s_{WC}^2}{M}\right]^2$$

Power

Two-Sided Test

The power of the two-sided test assuming $n = N_T = N_C$ is given by

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

where

$$R_1 = \frac{\sigma_{BT}^2}{\sigma_{BC}^2}$$

$$\sigma_{BT}^2 = R_1\sigma_{BC}^2$$

$$\sigma^{*2} = 2\left[\left(\sigma_{BT}^2 + \frac{\sigma_{WT}^2}{M}\right)^2 + R_0^2\left(\sigma_{BC}^2 + \frac{\sigma_{WC}^2}{M}\right)^2 + \frac{\sigma_{WT}^4}{M^2(M-1)} + \frac{R_0^2\sigma_{WC}^4}{M^2(M-1)}\right]$$

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

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

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

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

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains the parameters associated with this test such as the means, sample sizes, alpha, and power.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. Under most situations, you will select either *Power* or *Sample Size*.

Test Direction

Alternative Hypothesis

Specify whether the alternative hypothesis of the test is one-sided or two-sided.

Note that this parameter impacts the value of alpha. The value of alpha is used directly for one-sided tests. For two-sided tests, alpha is replaced by alpha/2.

Two-Sided Hypothesis Test

H0: $\sigma^2_{BT}/\sigma^2_{BC} = R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} \neq R0$

One-Sided Hypothesis Tests

Lower: H0: $\sigma^2_{BT}/\sigma^2_{BC} \geq R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} < R0$

Upper: H0: $\sigma^2_{BT}/\sigma^2_{BC} \leq R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} > R0$

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

Sample Size Per Group

The Sample Size Per Group is the number of items or individuals sampled in a group. Since the sample sizes are the same in each group, this value is the value for N_T and N_C.

The Sample Size Per Group must be ≥ 2. You can enter a single value or a series of values.

M (Measurements Per Subject)

Enter one or more values for M: the number of repeated measurements per subject. All measurements are for the same treatment.

You can enter a single value such as 2, a series of values such as 2 3 4, or 2 to 8 by 1.

The range is M ≥ 2.

Effect Size

R0 (H0 Variance Ratio)

Enter one or more values for the ratio of the two between-subject variances (σ^2_{BT} / σ^2_{BC}) assumed by the null hypothesis, H0. The sample variance ratio is compared to this value when conducting the test.

The usual equality test assumes this value is one. This procedure allows you to enter values other than one.

The range of possible values is $R0 > 0$. $R0 \neq R1$.

R1 (Actual Variance Ratio)

Enter one or more values for between-subject variance ratio assumed by the alternative hypothesis. This is the value of σ^2_{BT} / σ^2_{BC} at which the power is calculated.

The range of possible values is $R1 > 0$. $R1 \neq R0$.

σ^2_{BC} (Control Variance)

Enter one or more values for the between-subject variance of the control measurements. This value will have to be determined from a previous study or a pilot study.

The range of possible values is $\sigma^2_{BC} > 0$.

σ^2_{WT} (Treatment, Within-Subject Variance)

Enter one or more values for within-subject variance of the treatment measurements. This value will have to be determined from a previous study or a pilot study.

The range of possible values is $\sigma^2_{WT} > 0$.

σ^2_{WC} (Control, Within-Subject Variance)

Enter one or more values for within-subject variance of the control measurements. This value will have to be determined from a previous study or a pilot study.

The range of possible values is $\sigma^2_{WC} > 0$.

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 two-group, parallel 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 0.8, the significance level to 0.05, the power to 0.90, M to 2, and the actual variance ratio values between 0.5 and 1.3. They also set σ^2_{BC} = 0.8, σ^2_{WT} = 0.2, and σ^2_{WC} = 0.3. They want to investigate the range of required sample size values assuming that the two group sample sizes are equal.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Non-Unity Null Tests for Two Between Variances in a Replicated Design** procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided (H1: $\sigma^2_{BT}/\sigma^2_{BC}$ ≠ R0)**
Power	**0.90**
Alpha	**0.05**
M (Measurements Per Subject)	**2**
R0 (H0 Variance Ratio)	**0.8**
R1 (Actual Variance Ratio)	**0.5 0.7 0.9 1.1 1.3**
σ^2_{BC} (Control Variance)	**0.8**
σ^2_{WT} (Treatment Variance)	**0.2**
σ^2_{WC} (Control Variance)	**0.3**

Annotated Output

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

Numeric Results

H0: $\sigma^2_{BT}/\sigma^2_{BC}$ = R0 vs. H1: $\sigma^2_{BT}/\sigma^2_{BC}$ ≠ R0

Actual Power	Grp T Sample Size N_T	Grp C Sample Size N_C	N	Num Reps M	H0 Var Ratio R0	Actual Var Ratio R1	Betw Subj Var Cntl σ^2_{BC}	Wthn Subj Var Trt σ^2_{WT}	Wthn Subj Var Cntl σ^2_{WC}	Alpha
0.9001	311	311	622	2	0.800	0.500	0.800	0.200	0.300	0.050
0.9001	3408	3408	6816	2	0.800	0.700	0.800	0.200	0.300	0.050
0.9000	4185	4185	8370	2	0.800	0.900	0.800	0.200	0.300	0.050
0.9005	571	571	1142	2	0.800	1.100	0.800	0.200	0.300	0.050
0.9003	250	250	500	2	0.800	1.300	0.800	0.200	0.300	0.050

References

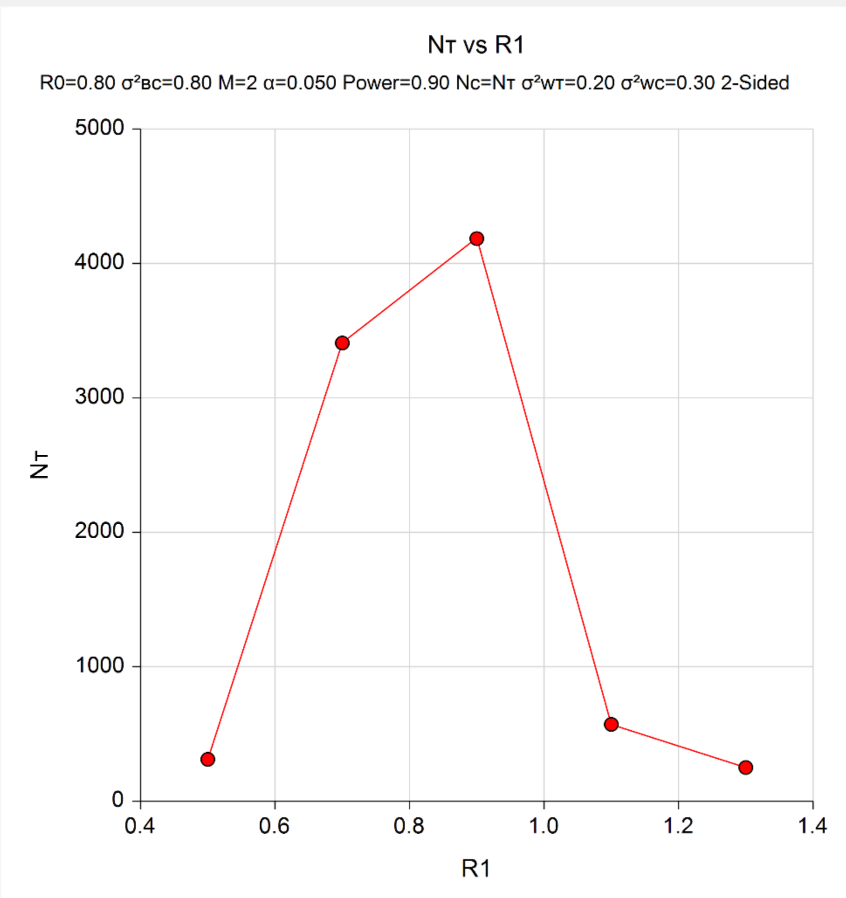
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Chow, S.C. and Liu, J.P. 2014. Design and Analysis of Clinical Trials, Third Edition. John Wiley & Sons. Hoboken, New Jersey.

Report Definitions
Actual Power is the actual power achieved. Because N_T and N_C are discrete, this value is usually slightly larger than the target power.
N_T is the number of subjects in the treatment group.
N_C is the number of subjects in the control group.
N is the total number of subjects. $N = N_T + N_C$.
M is the number of replicates. That is, it is the number of times a treatment measurement is repeated on a subject.
R0 is the between-subject variance ratio used to define the null hypothesis, H0.
R1 is the value of the between-subject variance ratio at which the power is calculated.
σ^2_{BC} is the between-subject variance of measurements in the control group. Note that $\sigma^2_{TC} = \sigma^2_{BC} + \sigma^2_{WC}$.
σ^2_{WT} is the within-subject variance of measurements in the treatment group.
σ^2_{WC} is the within-subject variance of measurements in the control group.
Alpha is the probability of rejecting a true null hypothesis, H0.

Summary Statements
A study is being conducted to compare the between-subject variance of a treatment group to a control group using a two-sided hypothesis test of data from a replicated parallel design. Group sample sizes of 311 and 311 achieve 90% power to reject the null hypothesis at a significance level of 0.050. The variance ratio assumed by the null hypothesis is 0.800. The variance ratio at which the power is calculated is 0.500. The number of times the measurement is repeated on a subject is 2. The actual between-subject variance of the control group is assumed to be 0.800. The actual within-subject variance of the treatment group is assumed to be 0.200. The actual within-subject variance of the control group is assumed to be 0.300.

This report gives the sample sizes for the indicated scenarios.

Plot Section



This plot shows the relationship between sample size and R1.

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

We will use an example from Chow *et al*. (2018) pages 212-213 to validate this procedure.

In this example, R0 = 1.21, power = 0.8, significance level = 0.05, M = 3, R1 = 0.5625, σ^2_{BC} = 0.16, σ^2_{WT} = 0.04, σ^2_{WC} = 0.09. The problem is to find the sample size for the lower, one-sided test (note that this is a non-inferiority test). They find the per group sample size to be approximately 74.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Non-Unity Null Tests for Two Between Variances in a Replicated Design** procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**One-Sided (H1: $\sigma^2_{BT}/\sigma^2_{BC}$ < R0)**
Power	**0.80**
Alpha	**0.05**
M (Measurements Per Subject)	**3**
R0 (H0 Variance Ratio)	**1.21**
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**

Output

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

Numeric Results

H0: $\sigma^2_{BT}/\sigma^2_{TC}$ ≥ R0 vs. H1: $\sigma^2_{BT}/\sigma^2_{BC}$ < R0

Actual Power	Grp T Sample Size N_T	Grp C Sample Size N_C	N	Num Reps M	H0 Var Ratio R0	Actual Var Ratio R1	Betw Subj Var Cntl σ^2_{BC}	Wthn Subj Var Trt σ^2_{WT}	Wthn Subj Var Cntl σ^2_{WC}	Alpha
0.8044	75	75	150	3	1.210	0.563	0.160	0.040	0.090	0.050

The sample size of 75 per group is close to their answer of 74. The difference occurs because of rounding. The sample size of 74 per group actually has a power slightly less than 0.8.