Chapter 309

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

Introduction

This procedure calculates power and sample size of tests of total 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 total 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 one 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 221 - 224.

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

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

where

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

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Similarly, the between-subject variances are estimated as

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

where

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

Now, estimators for the total variance are given by

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

Testing Variance Inequality with a Non-Unity Null

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

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

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

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

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

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

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 $\hat{\eta}_U < 0$.

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The $\Delta's$ are given by

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

$$+ h\left(\frac{\alpha}{2}, N_C(M-1)\right)\left[\frac{(M-1)R_0 s_{WC}^2}{M}\right]^2$$

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

$$+ h\left(1 - \frac{\alpha}{2}, N_C(M-1)\right)\left[\frac{(M-1)R_0 s_{WC}^2}{M}\right]^2$$

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

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

$$+ h\big(1 - \alpha, N_C(M-1)\big)\left[\frac{(M-1)R_0 s_{WC}^2}{M}\right]^2$$

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Power

Two-Sided Test

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

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

where

$$R_1 = \frac{\sigma_{TT}^2}{\sigma_{TC}^2}$$

$$\sigma_{TT}^2 = R_1\sigma_{TC}^2$$

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

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, $H_0: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \geq R0$ versus $H_1: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} < R0$, is given by

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

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

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

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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 total variability. A two-group, parallel 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 1.3. They also set σ^2_{TC} = 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

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: $\sigma^2_{TT}/\sigma^2_{TC} \neq$ 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_{TC} (Control Variance)	**0.8**
σ^2_{WT} (Treatment Variance)	**0.2**
σ^2_{WC} (Control Variance)	**0.3**

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Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Hypotheses: H0: $\sigma^2_{TT}/\sigma^2_{TC}$ = R0 vs. H1: $\sigma^2_{TT}/\sigma^2_{TC} \neq$ R0

Power		Sample Size				Total Variance			Within-Subject Variance		
						Ratio					
Target	Actual	Treatment N_T	Control N_C	Total N	Measurements per Subject M	H0 (Null) R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.9	0.9012	141	141	282	2	0.8	0.5	0.8	0.2	0.3	0.05
0.9	0.9000	1663	1663	3326	2	0.8	0.7	0.8	0.2	0.3	0.05
0.9	0.9001	2231	2231	4462	2	0.8	0.9	0.8	0.2	0.3	0.05
0.9	0.9004	330	330	660	2	0.8	1.1	0.8	0.2	0.3	0.05
0.9	0.9004	155	155	310	2	0.8	1.3	0.8	0.2	0.3	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 N_T and N_C are discrete, this value is usually slightly larger than the target power.
N_T The number of subjects in the treatment group.
N_C The number of subjects in the control group.
N The total number of subjects. N = N_T + N_C.
M The number of replicates. That is, it is the number of times a treatment measurement is repeated on a subject.
R0 The total variance ratio used to define the null hypothesis, H0.
R1 The value of the total variance ratio at which the power is calculated. R1 = σ^2_{TT} / σ^2_{TC}.
σ^2_{TT} The total variance of measurements in the treatment group. Note that $\sigma^2_{TT} = \sigma^2_{BT} + \sigma^2_{WT}$.
σ^2_{TC} The total variance of measurements in the control group. Note that $\sigma^2_{TC} = \sigma^2_{BC} + \sigma^2_{WC}$.
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.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group replicated design will be used to test whether the total variance ratio (σ^2_{TT} / σ^2_{TC} = σ^2Total,Treatment / σ^2Total,Control) is different from 0.8 (H0: σ^2_{TT} / σ^2_{TC} = 0.8 versus H1: σ^2_{TT} / $\sigma^2_{TC} \neq$ 0.8). 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. Each subject will be measured 2 times. For the control group, the total variance (σ^2_{TC}) is assumed to be 0.8, 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. To detect a total variance ratio (σ^2_{TT} / σ^2_{TC}) of 0.5 with 90% power, the number of subjects needed will be 141 in the treatment group, and 141 in the control group.

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Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	**NT**	**Nc**	**N**	**NT'**	**Nc'**	**N'**	**DT**	**Dc**	**D**
20%	141	141	282	177	177	354	36	36	72
20%	1663	1663	3326	2079	2079	4158	416	416	832
20%	2231	2231	4462	2789	2789	5578	558	558	1116
20%	330	330	660	413	413	826	83	83	166
20%	155	155	310	194	194	388	39	39	78

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.
NT, Nc, and N The evaluable sample sizes at which power is computed. If NT and Nc subjects are evaluated out of the NT' and Nc' subjects that are enrolled in the study, the design will achieve the stated power.
NT', Nc', and N' The number of subjects that should be enrolled in the study in order to obtain NT, Nc, and N evaluable subjects, based on the assumed dropout rate. After solving for NT and Nc, NT' and Nc' are calculated by inflating NT and Nc using the formulas NT' = NT / (1 - DR) and Nc' = Nc / (1 - DR), with NT' and Nc' 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.)
DT, Dc, and D The expected number of dropouts. DT = NT' - NT, Dc = Nc' - Nc, and D = DT + Dc.

Dropout Summary Statements

Anticipating a 20% dropout rate, 177 subjects should be enrolled in Group 1, and 177 in Group 2, to obtain final group sample sizes of 141 and 141, 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.

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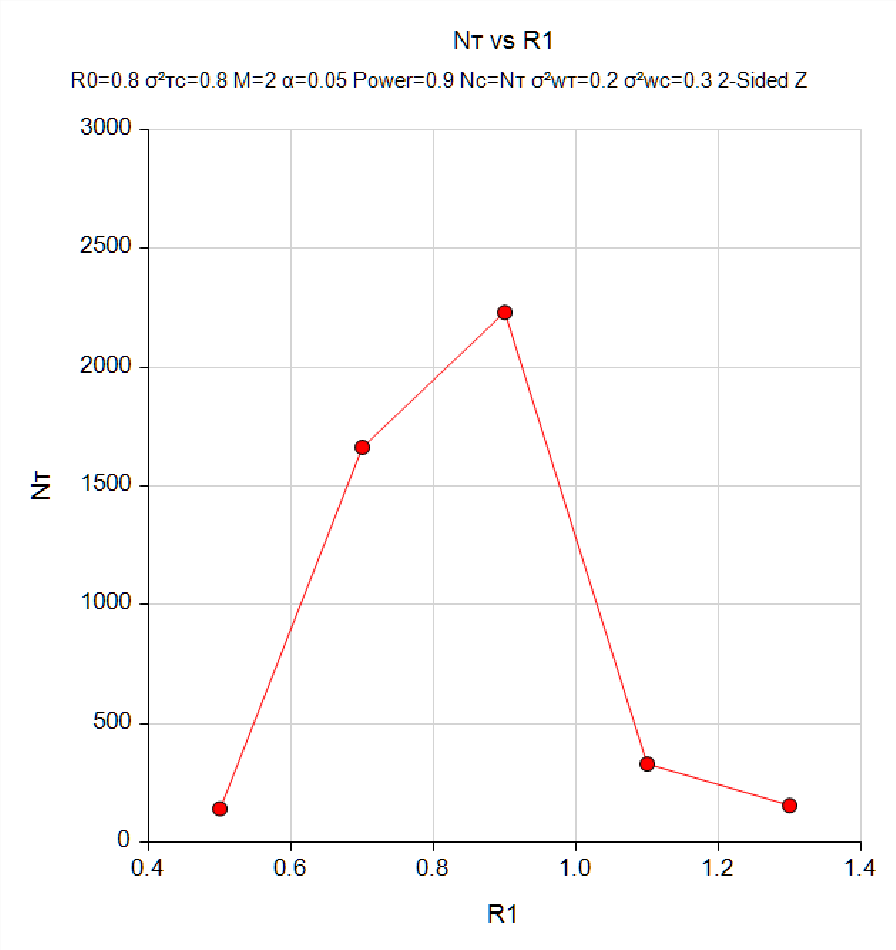
Plots Section

Plots



This plot shows the relationship between sample size and R1.

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

We will use an example from Chow *et al*. (2018) pages 223-224 to validate this procedure.

In this example, R0 = 1.21, significance level = 0.05, M = 3, R1 = 0.52, σ^2_{TC} = 0.25, 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 28.

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: $\sigma^2_{TT}/\sigma^2_{TC}$ < R0)**
Power... **0.8**
Alpha.. **0.05**
M (Measurements Per Subject) **3**
R0 (H0 Variance Ratio)................................. **1.21**
R1 (Actual Variance Ratio) **0.52**
σ^2_{TC} (Control Variance)................................. **0.25**
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

Solve For: Sample Size
Hypotheses: H0: $\sigma^2_{TT}/\sigma^2_{TC} \geq$ R0 vs. H1: $\sigma^2_{TT}/\sigma^2_{TC}$ < R0

Power		Sample Size				Total Variance			Within-Subject Variance		
						Ratio					
Target	Actual	Treatment N_T	Control N_C	Total N	Measurements per Subject M	H0 (Null) R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.8	0.8044	28	28	56	3	1.21	0.52	0.25	0.04	0.09	0.05

The sample size of 28 per group matches Chow *et al.* (2018).

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