Chapter 308

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 one. This is the common case. This routine expresses the effect size 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

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

where

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

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

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

$$H_0: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \geq 1 \quad \text{versus} \quad H_1: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} < 1,$$

$$H_0: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \leq 1 \quad \text{versus} \quad H_1: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} > 1,$$

$$H_0: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} = 1 \quad \text{versus} \quad H_1: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \neq 1.$$

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

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

The $\Delta's$ are given by

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

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

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

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

Power

Two-Sided Test

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

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

where

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

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

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

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, $H_0\!: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \geq 1$ versus $H_1\!: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} < 1,$ is given by

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

The power of the upper, one-sided test, $H_0\!: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \leq 1$ versus $H_1\!: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} > 1,$ is given by

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

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 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: $\sigma^2_{TT}/\sigma^2_{TC} \neq 1$)**
Power	**0.90**
Alpha	**0.05**
M (Measurements Per Subject)	**2**
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**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Hypotheses: H0: $\sigma^2_{TT}/\sigma^2_{TC} = 1$ vs. H1: $\sigma^2_{TT}/\sigma^2_{TC} \neq 1$

Power		Sample Size			Measurements	Total Variance		Within-Subject Variance		
Target	Actual	Treatment N_T	Control N_C	Total N	per Subject M	Ratio R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.9	0.9016	72	72	144	2	0.5	0.8	0.2	0.3	0.05
0.9	0.9009	244	244	488	2	0.7	0.8	0.2	0.3	0.05
0.9	0.9001	2757	2757	5514	2	0.9	0.8	0.2	0.3	0.05
0.9	0.9000	3492	3492	6984	2	1.1	0.8	0.2	0.3	0.05
0.9	0.9004	489	489	978	2	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.
R1 The value of the total variance ratio at which the power is calculated. $R1 = \sigma^2_{TT} / \sigma^2_{TC}$.
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 of the treatment (σ^2_{TT}) is different from the total variance of the control (σ^2_{TC}) by testing whether the total variance ratio ($\sigma^2_{TT} / \sigma^2_{TC}$) is different from 1 (H0: $\sigma^2_{TT} / \sigma^2_{TC} = 1$ versus H1: $\sigma^2_{TT} / \sigma^2_{TC} \neq 1$). 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 ($\sigma^2_{TT} / \sigma^2_{TC}$) of 0.5 with 90% power, the number of subjects needed will be 72 in the treatment group, and 72 in the control group.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	**N_T**	**N_C**	**N**	**N_T'**	**N_C'**	**N'**	**D_T**	**D_C**	**D**
20%	72	72	144	90	90	180	18	18	36
20%	244	244	488	305	305	610	61	61	122
20%	2757	2757	5514	3447	3447	6894	690	690	1380
20%	3492	3492	6984	4365	4365	8730	873	873	1746
20%	489	489	978	612	612	1224	123	123	246

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

Dropout Summary Statements

Anticipating a 20% dropout rate, 90 subjects should be enrolled in Group 1, and 90 in Group 2, to obtain final group sample sizes of 72 and 72, respectively.

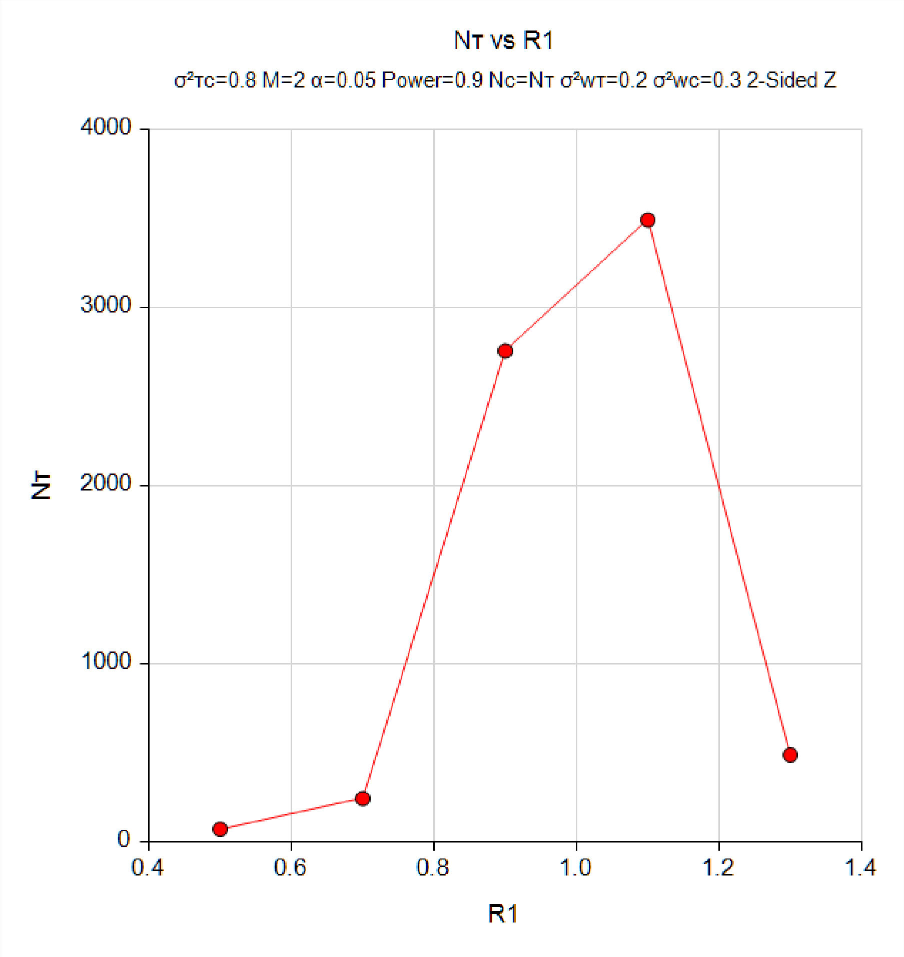
References

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 PASS

We will use an example from a previously validated **PASS** procedure to validate this procedure. The previously validated procedure is **Non-Unity Null Tests for Two Total Variances in a Replicated Design**.

For this example, if in the other procedure we set power = 0.8, R0 = 1, 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 resulting per group sample size is 43.

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: $\sigma^2_{TT}/\sigma^2_{TC}$ < 1)**
Power... **0.80**
Alpha.. **0.05**
M (Measurements Per Subject) **3**
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: $\sigma^2_{TT}/\sigma^2_{TC} \geq 1$ vs. H1: $\sigma^2_{TT}/\sigma^2_{TC} < 1$

Power		Sample Size			Measurements	Total Variance		Within-Subject Variance		
Target	Actual	Treatment N_T	Control N_C	Total N	per Subject M	Ratio R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.8	0.808	43	43	86	3	0.52	0.25	0.04	0.09	0.05

The sample size of 43 per group matches the expected result.