Chapter 316

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

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

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

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

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

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

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

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

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 $\Delta's$ are given by

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

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

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

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

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

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

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

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

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, $H_0: \frac{\sigma_{BT}^2}{\sigma_{BC}^2} \geq 1 \text{ versus } H_1: \frac{\sigma_{BT}^2}{\sigma_{BC}^2} < 1,$ is given by

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

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

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

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 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 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

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: $\sigma^2_{BT}/\sigma^2_{BC} \neq 1$)**
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_{BC} (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: $\sigma^2_{BT}/\sigma^2_{BC} = 1$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} \neq 1$

Power		Sample Size			Measurements	Between-Subject Variance		Within-Subject Variance		
Target	Actual	Treatment N_T	Control N_C	Total N	per Subject M	Ratio R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.9	0.9007	156	156	312	2	0.5	0.8	0.2	0.3	0.05
0.9	0.9005	501	501	1002	2	0.7	0.8	0.2	0.3	0.05
0.9	0.9001	5279	5279	10558	2	0.9	0.8	0.2	0.3	0.05
0.9	0.9000	6224	6224	12448	2	1.1	0.8	0.2	0.3	0.05
0.9	0.9003	816	816	1632	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 times a subject is measured. It is the number of repeated measurements.
R1 The value of the between-subject variance ratio at which the power is calculated. $R1 = \sigma^2_{BT} / \sigma^2_{BC}$.
σ^2_{BC} The between-subject 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 between-subject variance of the treatment (σ^2_{BT}) is different from the between-subject variance of the control (σ^2_{BC}) by testing whether the between-subject variance ratio ($\sigma^2_{BT} / \sigma^2_{BC}$) is different from 1 (H0: $\sigma^2_{BT} / \sigma^2_{BC} = 1$ versus H1: $\sigma^2_{BT} / \sigma^2_{BC} \neq 1$). 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 between-subject variance (σ^2_{BC}) 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 between-subject variance ratio ($\sigma^2_{BT} / \sigma^2_{BC}$) of 0.5 with 90% power, the number of subjects needed will be 156 in the treatment group, and 156 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%	156	156	312	195	195	390	39	39	78
20%	501	501	1002	627	627	1254	126	126	252
20%	5279	5279	10558	6599	6599	13198	1320	1320	2640
20%	6224	6224	12448	7780	7780	15560	1556	1556	3112
20%	816	816	1632	1020	1020	2040	204	204	408

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, 195 subjects should be enrolled in Group 1, and 195 in Group 2, to obtain final group sample sizes of 156 and 156, respectively.

References

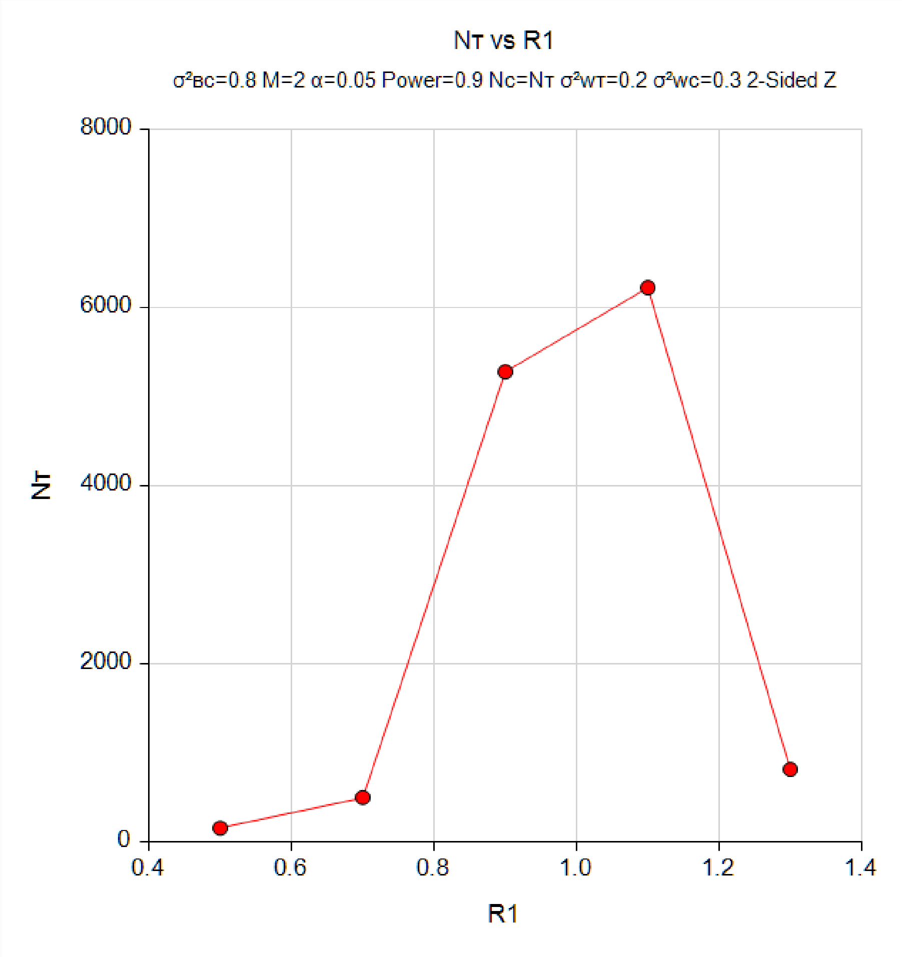
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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 Between 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_{BC} = 0.25, σ^2_{WT} = 0.04, σ^2_{WC} = 0.09, the resulting per group sample size is 109.

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 .... **Two-Sided (H1: $\sigma^2_{BT}/\sigma^2_{BC} \neq 1$)**
Power.. **0.80**
Alpha.. **0.05**
M (Measurements Per Subject) **3**
R1 (Actual Variance Ratio) **0.52**
σ^2_{BC} (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: $\sigma^2_{BT}/\sigma^2_{BC} = 1$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} \neq 1$

Power		Sample Size			Measurements	Between-Subject Variance		Within-Subject Variance		
Target	Actual	Treatment N_T	Control N_C	Total N	per Subject M	Ratio R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.8	0.802	109	109	218	3	0.52	0.25	0.04	0.09	0.05

The sample size of 109 per group matches the expected result.