Chapter 319

Superiority by a Margin Tests for Two Between Variances in a Replicated Design

Introduction

This procedure calculates power and sample size of tests of superiority by a margin 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 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 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 Superiority by a Margin

The following statistical hypotheses are used to test for between-subject variance superiority by a margin.

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

where *R0* is the superiority limit.

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

Superiority by a Margin Test

For the superiority by a margin 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 is given by

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

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.

Power

Superiority by a Margin Test

The power of the superiority by a margin test is given by

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

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.

Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to show that it is superior to the standard drug in terms of the between-subject variability. A two-group, parallel design with replicates will be used to test the superiority.

Company researchers set the superiority limit to 0.8, the significance level to 0.05, the power to 0.90, M to 2, and the actual variance ratio values between 0.4 and 0.7. They also set $\sigma^2_{BC} = 0.8$, $\sigma^2_{WT} = 0.2$, and $\sigma^2_{WC} = 0.3$. 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**
Power	**0.90**
Alpha	**0.05**
M (Measurements Per Subject)	**2**
R0 (Superiority Variance Ratio)	**0.8**
R1 (Actual Variance Ratio)	**0.4 0.5 0.6 0.7**
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: $\sigma^2_{BT}/\sigma^2_{BC} \geq R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} < R0$

Power		Sample Size			Measurements	Between-Subject Variance Ratio			Within-Subject Variance		
Target	Actual	Treatment N_T	Control N_C	Total N	per Subject M	Superiority R0	Actual R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.9	0.9016	131	131	262	2	0.8	0.4	0.8	0.2	0.3	0.05
0.9	0.9007	254	254	508	2	0.8	0.5	0.8	0.2	0.3	0.05
0.9	0.9001	628	628	1256	2	0.8	0.6	0.8	0.2	0.3	0.05
0.9	0.9000	2777	2777	5554	2	0.8	0.7	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 Nc are discrete, this value is usually slightly larger than the target power.
N_T	The number of subjects in the treatment group.
Nc	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.
R0	The superiority limit for the between-subject variance ratio.
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 superior to the between-subject variance of the control (σ^2_{BC}) by a margin by testing whether the between-subject variance ratio ($\sigma^2_{BT} / \sigma^2_{BC}$) is less than the superiority ratio 0.8 (H0: $\sigma^2_{BT} / \sigma^2_{BC} \geq 0.8$ versus H1: $\sigma^2_{BT} / \sigma^2_{BC} < 0.8$). The comparison will be made using a one-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 0.4 with 90% power, the number of subjects needed will be 131 in the treatment group, and 131 in the control group.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N_T	Nc	N	N_T'	Nc'	N'	D_T	Dc	D
20%	131	131	262	164	164	328	33	33	66
20%	254	254	508	318	318	636	64	64	128
20%	628	628	1256	785	785	1570	157	157	314
20%	2777	2777	5554	3472	3472	6944	695	695	1390

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

Dropout Summary Statements

Anticipating a 20% dropout rate, 164 subjects should be enrolled in Group 1, and 164 in Group 2, to obtain final group sample sizes of 131 and 131, respectively.

References

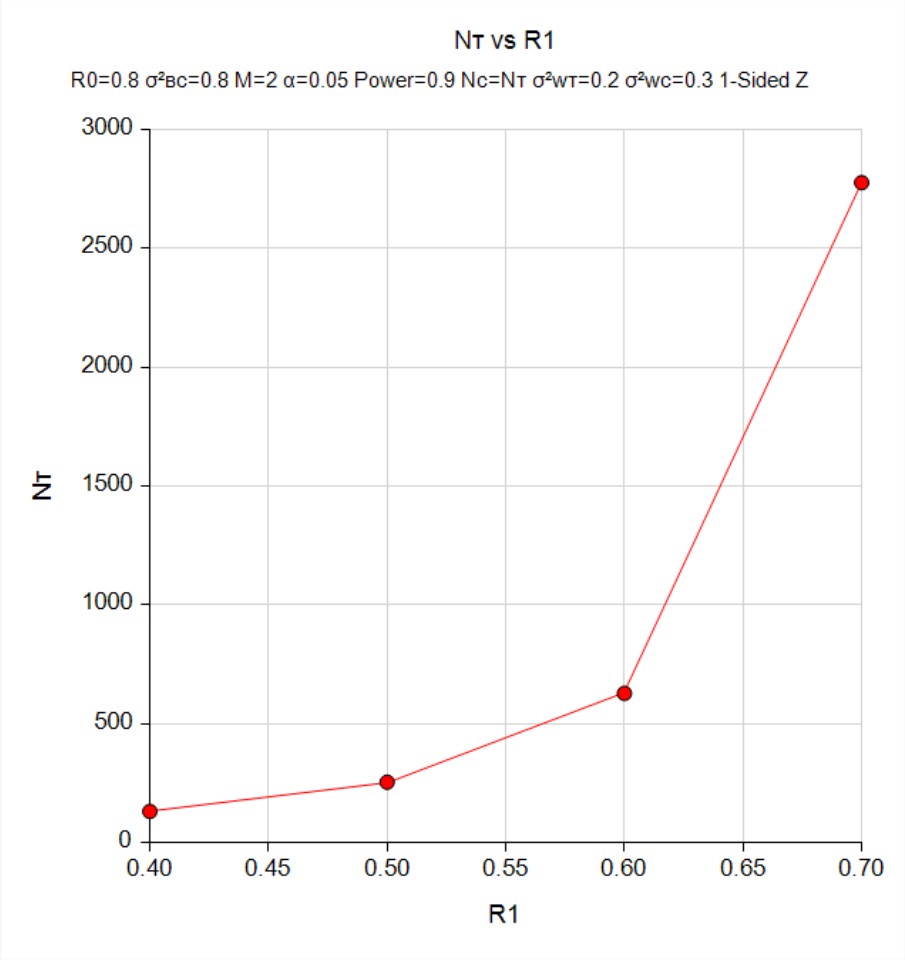
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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 = 0.80, R0 = 0.8, 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 180.

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**
Power	**0.80**
Alpha	**0.05**
M (Measurements Per Subject)	**3**
R0 (Superiority Variance Ratio)	**0.8**
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: $\sigma^2_{BT}/\sigma^2_{BC} \geq R0$ vs. H1: $\sigma^2_{BT}/\sigma^2_{BC} < R0$

Power		Sample Size			Measurements per Subject	Between-Subject Variance Ratio			Within-Subject Variance		
Target	Actual	Treatment N_T	Control N_C	Total N	M	Superiority R0	Actual R1	Control σ^2_{BC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Alpha
0.8	0.8011	180	180	360	3	0.8	0.52	0.25	0.04	0.09	0.05

The sample size of 180 per group matches the expected result.