

Chapter 311

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

Introduction

This procedure calculates power and sample size of tests of superiority by a margin 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 ($j = 1, \dots, N_i$), and k th replicate ($k = 1, \dots, M$). 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

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

where

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

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

Similarly, the between-subject variances are estimated as

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

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 Superiority by a Margin

The following statistical hypotheses are used to test for total variance superiority by a margin.

$$H_0: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \geq R_0 \quad \text{versus} \quad H_1: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} < R_0,$$

where R_0 is the superiority limit.

Let $\eta = \sigma_{TT}^2 - R_0(\sigma_{TC}^2)$ be the parameter of interest. The test statistic is $\hat{\eta} = \hat{\sigma}_{TT}^2 - R_0(\hat{\sigma}_{TC}^2)$.

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

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

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

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

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 R_1 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 total variability. A two-group, parallel design 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 $\sigma^2_{\tau c} = 0.8$, $\sigma^2_{\tau T} = 0.2$, and $\sigma^2_{\tau c} = 0.3$. 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
$\sigma^2_{\tau c}$ (Control Variance).....	0.8
$\sigma^2_{\tau T}$ (Treatment Variance)	0.2
$\sigma^2_{\tau c}$ (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: $H_0: \sigma^2_{TT}/\sigma^2_{TC} \geq R_0$ vs. $H_1: \sigma^2_{TT}/\sigma^2_{TC} < R_0$

Power		Sample Size			Measurements per Subject M	Total Variance			Within-Subject Variance		Alpha
						Ratio	Superiority R0	Actual R1	Control σ^2_{TC}	Treatment σ^2_{WT}	
Target	Actual	Treatment N _T	Control N _C	Total N							
0.9	0.9026	58	58	116	2	0.8	0.4	0.8	0.2	0.3	0.05
0.9	0.9013	115	115	230	2	0.8	0.5	0.8	0.2	0.3	0.05
0.9	0.9001	294	294	588	2	0.8	0.6	0.8	0.2	0.3	0.05
0.9	0.9001	1356	1356	2712	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 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 superiority by a margin limit for the total variance ratio.
- R₁ The value of the total variance ratio at which the power is calculated. $R_1 = \sigma^2_{TT} / \sigma^2_{TC}$.
- 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 superior to the total variance of the control (σ^2_{TC}) by a margin by testing the total variance ratio ($\sigma^2_{TT} / \sigma^2_{TC}$) against the superiority ratio 0.8 ($H_0: \sigma^2_{TT} / \sigma^2_{TC} \geq 0.8$ versus $H_1: \sigma^2_{TT} / \sigma^2_{TC} < 0.8$). 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 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 0.4 with 90% power, the number of subjects needed will be 58 in the treatment group, and 58 in the control group.

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

Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	N _T	N _c	N	N _T '	N _c '	N'	D _T	D _c	D
20%	58	58	116	73	73	146	15	15	30
20%	115	115	230	144	144	288	29	29	58
20%	294	294	588	368	368	736	74	74	148
20%	1356	1356	2712	1695	1695	3390	339	339	678

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 Lohknygina, 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, 73 subjects should be enrolled in Group 1, and 73 in Group 2, to obtain final group sample sizes of 58 and 58, respectively.

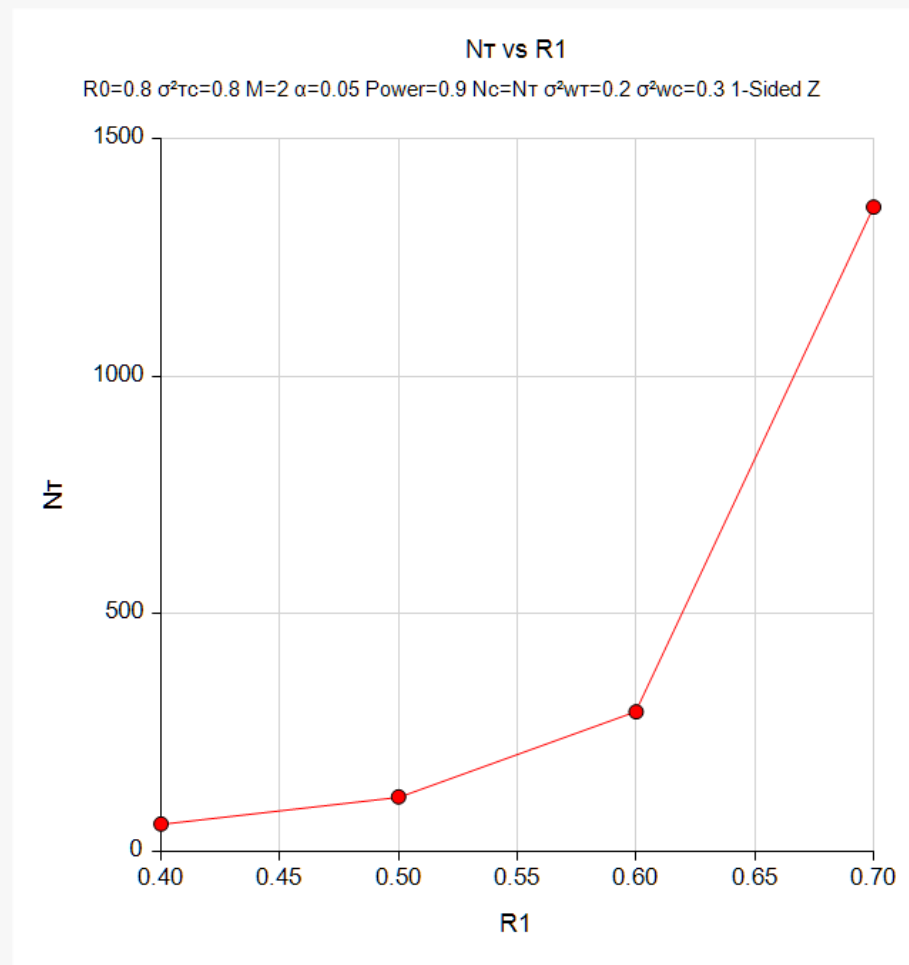
References

- Chow, S.C., Shao, J., Wang, H., and Lohknygina, 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 = 0.80, R0 = 0.8, significance level = 0.05, M = 3, R1 = 0.52, $\sigma^2_{TC} = 0.25$, $\sigma^2_{WT} = 0.04$, $\sigma^2_{WC} = 0.09$, the resulting per group sample size is 90.

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_{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: $H_0: \sigma^2_{TT}/\sigma^2_{TC} \geq R_0$ vs. $H_1: \sigma^2_{TT}/\sigma^2_{TC} < R_0$												
Power		Sample Size			Measurements per Subject M	Total Variance			Within-Subject Variance		Alpha	
Target	Actual	Treatment N _T	Control N _C	Total N		Ratio		Treatment σ^2_{WT}	Control σ^2_{WC}			
					Superiority R ₀	Actual R ₁	Control σ^2_{TC}					
0.8	0.8037	90	90	180	3	0.8	0.52	0.25	0.04	0.09	0.05	

The sample size of 90 per group matches the expected result.