Chapter 312

Tests for Two Total Variances in a 2×2 Cross-Over Design

Introduction

This procedure calculates power and sample size of tests of total variabilities (between + within) from a 2×2 cross-over design for the case when the ratio assumed by the null hypothesis is one. This routine deals with the case in which the statistical hypotheses are expressed in terms of the ratio of the total variances.

This design is used to compare two treatments which are administered to subjects in different orders. The design has two treatment sequences. The two sequences are

sequence 1: C T

sequence 2: T C

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 224 - 227.

Suppose x_{ijk} is the response in the ith sequence (i = 1, 2), j^{th} subject (j = 1, ..., Ni), and k^{th} treatment (k = T, C). The mixed effect model analyzed in this procedure is

$$x_{ijk} = \mu_k + \gamma_{ik} + S_{ijk} + e_{ijk}$$

where μ_k is the kth treatment effect, γ_{ik} is the interaction between sequence i and treatment k, S_{ijT} and S_{ijC} are random effects of the ij^{th} subject, and e_{ijk} is the within-subject error term which is normally distributed with mean 0 and variance $V_k = \sigma_{Wk}^2$.

Let $N_s = N_1 + N_2 - 2$. The total variances ($\sigma_{Tk}^2 = \sigma_{Bk}^2 + \sigma_{Wk}^2,\ k = T, C$) are estimated by

$$\hat{\sigma}_{TK}^2 = s_{Tk}^2 = \frac{1}{N_S}\sum_{i=1}^{2}\sum_{j=1}^{N_i}\left(\bar{x}_{ijk} - \bar{x}_{i.k}\right)^2$$

where

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

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The sample between-subject covariance is calculated using

$$s_{BTC}^2 = \frac{1}{N_S}\sum_{i=1}^{2}\sum_{j=1}^{N_i}\left(\bar{x}_{ijT} - \bar{x}_{i.T}\right)\left(\bar{x}_{ijC} - \bar{x}_{i.C}\right)$$

Using this value, the sample between-subject correlation is easily calculated.

Testing Variance Inequality

The following three sets of statistical hypotheses are used to test for total variance inequality

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

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

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

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

$$\Delta_L = h\left(1 - \frac{\alpha}{2}, N_s\right)\lambda_1^2 + h\left(\frac{\alpha}{2}, N_s\right)\lambda_2^2$$

$$\Delta_U = h\left(\frac{\alpha}{2}, N_s\right)\lambda_1^2 + h\left(1 - \frac{\alpha}{2}, N_s\right)\lambda_2^2$$

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where

$$h(A,B) = \left(1 - \frac{B}{\chi^2_{A,B}}\right)^2$$

$$\lambda_i^2 = \left(\frac{s_{TT}^2 - s_{TC}^2 \pm \sqrt{(s_{TT}^2 + s_{TC}^2)^2 - 4s_{BTC}^4}}{2}\right) \text{ for } i = 1,2$$

and $\chi^2_{A,B}$ 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

$$\Delta_U = h(\alpha, N_s - 1)\lambda_1^2 + h(1-\alpha, N_s - 1)\lambda_2^2$$

Power

Two-Sided Test

The power of the two-sided test is given by

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

where

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

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

$$\sigma^{*2} = 2[\sigma_{TT}^4 + \sigma_{TC}^4 - 2\sigma_{BT}^2\sigma_{BC}^2\rho^2]$$

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.

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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

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

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

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

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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 2 x 2 cross-over 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, and the actual variance ratio values between 0.5 and 1.3. They also set $\sigma^2_{TC} = 0.8$, $\sigma^2_{WT} = 0.2$, $\sigma^2_{WC} = 0.3$, and $\rho = 0.7$. They want to investigate the range of required sample size values assuming that the two sequence 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**
Sequence Allocation	**Equal (N1 = N2)**
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**
ρ (Treatment, Control Correlation)	**0.7**

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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: $\sigma^2_{TT}/\sigma^2_{TC} = 1$ vs. H1: $\sigma^2_{TT}/\sigma^2_{TC} \neq 1$

Power		Sequence Sample Size			Total Variance		Within-Subject Variance		Between-Subject (Treatment, Control)	
Target	Actual	N1	N2	N	Ratio R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	Correlation ρ	Alpha
0.9	0.9054	48	48	96	0.5	0.8	0.2	0.3	0.7	0.05
0.9	0.9004	143	143	286	0.7	0.8	0.2	0.3	0.7	0.05
0.9	0.9001	1485	1485	2970	0.9	0.8	0.2	0.3	0.7	0.05
0.9	0.9001	1777	1777	3554	1.1	0.8	0.2	0.3	0.7	0.05
0.9	0.9000	240	240	480	1.3	0.8	0.2	0.3	0.7	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 N1 and N2 are discrete, this value is usually slightly larger than the target power.
N1 The number of subjects in sequence 1.
N2 The number of subjects in sequence 2.
N The total number of subjects. N = N1 + N2.
R1 The value of the total variance ratio (treatment / control) 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.
ρ The between-subject correlation of the treatment and control.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A 2×2 cross-over 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 (σ^2_{TT} / σ^2_{TC}) is different from 1 (H0: σ^2_{TT} / σ^2_{TC} = 1 versus H1: σ^2_{TT} / $\sigma^2_{TC} \neq 1$). Each subject will alternate treatments (T and C), with an assumed wash-out period between measurements to avoid carry-over. For those in the Sequence 1 group, the first treatment will be C, and the sequence is [C T]. For those in the Sequence 2 group, the first treatment will be T, and the sequence is [T C]. 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. 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. The between-subject correlation between the treatment and control measurements per subject is assumed to be 0.7. 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 48 in Group/Sequence 1, and 48 in Group/Sequence 2.

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Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	**N1**	**N2**	**N**	**N1'**	**N2'**	**N'**	**D1**	**D2**	**D**
20%	48	48	96	60	60	120	12	12	24
20%	143	143	286	179	179	358	36	36	72
20%	1485	1485	2970	1857	1857	3714	372	372	744
20%	1777	1777	3554	2222	2222	4444	445	445	890
20%	240	240	480	300	300	600	60	60	120

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.
N1, N2, and N The evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.
N1', N2', and N' The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' 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.)
D1, D2, and D The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements

Anticipating a 20% dropout rate, 60 subjects should be enrolled in Group 1, and 60 in Group 2, to obtain final group sample sizes of 48 and 48, 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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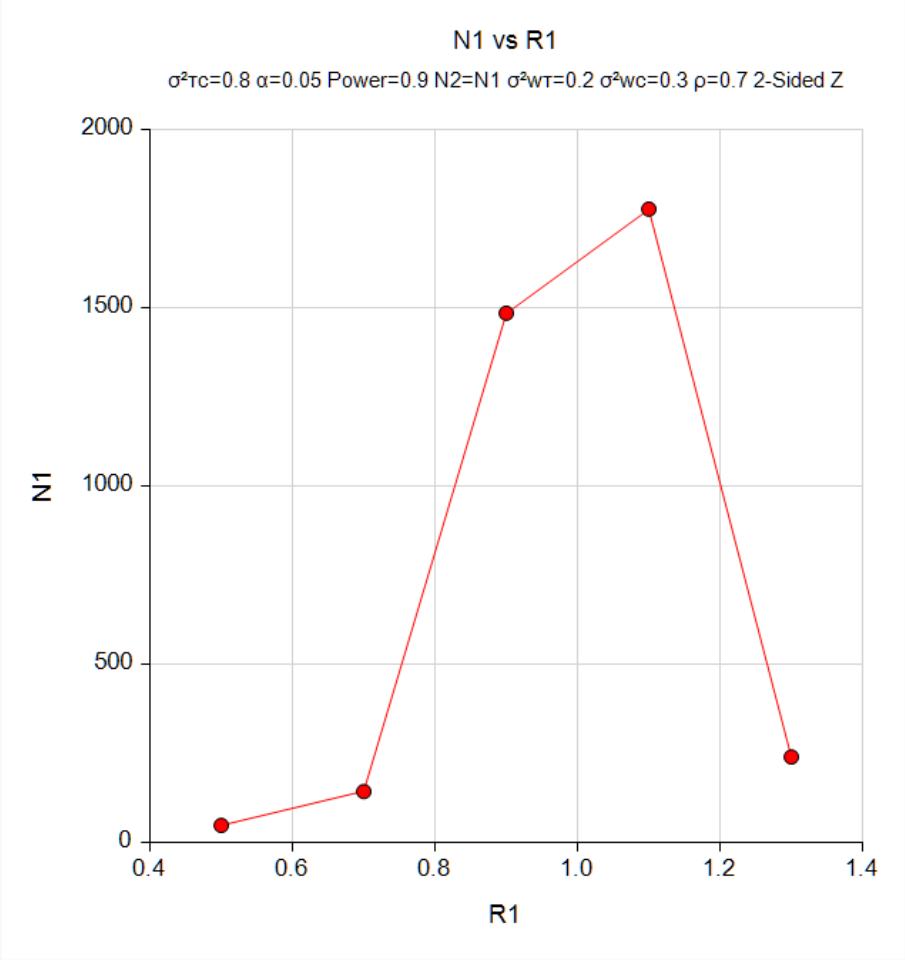
Plots Section

Plots



This plot shows the relationship between sample size and R1.

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Example 2 – Validation using another PASS Procedure

We previously validated the **Non-Unity Null Tests for Two Total Variances in a 2×2 Cross-Over Design** procedure which can be used to run this example. Hence, we will run an example through that procedure and use it to validate this procedure.

In the **Non-Unity Null Tests for Two Total Variances in a 2×2 Cross-Over Design procedure,** set the variance ratio under the null hypothesis to 1.0, the significance level to 0.05, the power to 0.80, and the actual variance ratio values to 1.2. They also set σ^2_{TC} = 0.8, σ^2_{WT} = 0.2, σ^2_{WC} = 0.3, and ρ =0.7. The sample size is computed as 366 per sequence for the two-sided case.

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: $\sigma^2_{TT}/\sigma^2_{TC} \neq 1$)**
Power..... **0.80**
Alpha..... **0.05**
Sequence Allocation ..... **Equal (N1 = N2)**
R1 (Actual Variance Ratio) **1.2**
σ^2_{TC} (Control Variance)..... **0.8**
σ^2_{WT} (Treatment Variance) **0.2**
σ^2_{WC} (Control Variance)..... **0.3**
ρ (Treatment, Control Correlation)..... **0.7**

Output

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

Numeric Results

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

Power		Sequence Sample Size			Total Variance		Within-Subject Variance		Between-Subject (Treatment, Control) Correlation	
Target	Actual	N1	N2	N	Ratio R1	Control σ^2_{TC}	Treatment σ^2_{WT}	Control σ^2_{WC}	ρ	Alpha
0.8	0.8004	366	366	732	1.2	0.8	0.2	0.3	0.7	0.05

The sample size of 366 per sequence matches the expected result.

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