Chapter 146

Non-Zero Null Tests for the Difference of Two Within-Subject CV's in a Parallel Design

Introduction

This procedure calculates power and sample size of inequality tests with a non-zero null difference of within-subject coefficients of variation (CV) from a parallel design with replicates (repeated measurements) of a particular treatment. This routine deals with the case in which the statistical hypotheses are expressed in terms of the difference of the within-subject CVs, which is the standard deviation divided by the mean.

Technical Details

This procedure uses the formulation first given by Quan and Shih (1996). The sample size formulas are given in Chow, Shao, Wang, and Lokhnygina (2018).

Suppose x_{ijk} is the response in the *i*th group or treatment (*i* = 1, 2), *j*th subject (*j* = 1, ..., *Ni*), and *k*th measurement (*k* = 1, ..., M). The simple one-way random mixed effects model leads to the following estimates of CV1 and CV2

$$\widehat{CV}_i = \frac{\hat{\sigma}_i}{\hat{\mu}_i}$$

$$\hat{\mu}_i = \frac{1}{N_i M}\sum_{j=1}^{N_i}\sum_{k=1}^{M} x_{ijk}$$

$$\hat{\sigma}_i^2 = \frac{1}{N_i(M-1)}\sum_{j=1}^{N_i}\sum_{k=1}^{M}\left(x_{ijk} - \bar{x}_{ij.}\right)^2$$

where

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

Testing Inequality (Two-Sided)

The following hypotheses are usually used to test for the inequality of CV

$$H_0: CV_1 - CV_2 = D0 \quad \text{versus} \quad H_1: CV_1 - CV_2 \neq D0.$$

The two-sided test statistic used to test this hypothesis is

$$T = \frac{\left(\widehat{CV}_1 - \widehat{CV}_2\right) - D0}{\sqrt{\frac{\hat{\sigma}_1^{*2}}{N_1} + \frac{\hat{\sigma}_2^{*2}}{N_2}}}$$

where *D*0 is the hypothesized CV difference under the null hypothesis and

$$\hat{\sigma}_i^{*2} = \frac{1}{2M}\widehat{CV}_i^2 + \widehat{CV}_i^4$$

T is asymptotically distributed as a standard normal random variable.

Hence the null hypothesis is rejected if $T < z_{\alpha/2}$ or $T > z_{1-\alpha/2}$.

Power

The power of this test is given by

$$\text{Power} = \Phi\left(z_{\alpha/2} - \mu_z\right) + 1 - \Phi\left(z_{1-\alpha/2} - \mu_z\right)$$

where

$$\sigma_i^{*2} = \frac{1}{2M}CV_i^2 + CV_i^4$$

$$\mu_z = \frac{(CV_1 - CV_2) - D0}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}}$$

and $\Phi(x)$ is the standard normal CDF.

A simple binary search algorithm can be applied to this power function to obtain an estimate of the necessary sample size.

Testing Inequality (Upper One-Sided)

The following hypotheses are usually used to test for the inequality of CV

$$H_0: CV_1 - CV_2 \leq D0 \quad \text{versus} \quad H_1: CV_1 - CV_2 > D0.$$

The one-sided test statistic used to test this hypothesis is

$$T = \frac{\left(\widehat{CV}_1 - \widehat{CV}_2\right) - D0}{\sqrt{\frac{\hat{\sigma}_1^{*2}}{N_1} + \frac{\hat{\sigma}_2^{*2}}{N_2}}}$$

where *D*0 is the hypothesized CV difference under the null hypothesis and

$$\hat{\sigma}_i^{*2} = \frac{1}{2M}\widehat{CV}_i^2 + \widehat{CV}_i^4$$

T is asymptotically distributed as a standard normal random variable.

Hence the null hypothesis is rejected if $T > z_{1-\alpha}$.

Power

The power of this combination of tests is given by

$$\text{Power} = 1 - \Phi(z_{1-\alpha} - \mu_z)$$

where

$$\sigma_i^{*2} = \frac{1}{2M}CV_i^2 + CV_i^4$$

$$\mu_z = \frac{(CV_1 - CV_2) - D0}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}}$$

and $\Phi(x)$ is the standard normal CDF.

A simple binary search algorithm can be applied to this power function to obtain an estimate of the necessary sample size.

Testing Inequality (Lower One-Sided)

The following hypotheses are usually used to test for the inequality of CV

$$H_0: CV_1 - CV_2 \geq D0 \quad \text{versus} \quad H_1: CV_1 - CV_2 < D0.$$

The one-sided test statistic used to test this hypothesis is

$$T = \frac{\left(\widehat{CV}_1 - \widehat{CV}_2\right) - D0}{\sqrt{\frac{\hat{\sigma}_1^{*2}}{N_1} + \frac{\hat{\sigma}_2^{*2}}{N_2}}}$$

where *D*0 is the hypothesized CV difference under the null hypothesis and

$$\hat{\sigma}_i^{*2} = \frac{1}{2M}\widehat{CV}_i^2 + \widehat{CV}_i^4$$

T is asymptotically distributed as a standard normal random variable.

Hence the null hypothesis is rejected if $T < z_\alpha$.

Power

The power of this combination of tests is given by

$$\text{Power} = \Phi(z_\alpha - \mu_z)$$

where

$$\sigma_i^{*2} = \frac{1}{2M}CV_i^2 + CV_i^4$$

$$\mu_z = \frac{(CV_1 - CV_2) - D0}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}}$$

and $\Phi(x)$ is the standard normal CDF.

A simple binary search algorithm can be applied to this 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 has a different within-subject CV from the standard drug. A parallel design with 2 repeated measurements per subject will be used.

Company researchers set the significance level to 0.05, the power to 0.90, CV2 to 0.4, D0 to -0.2, and D1 to -0.15 or -0.1 or -0.05 or 0. 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: CV1-CV2 ≠ D0)**
Power.. **0.90**
Alpha... **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **2**
Input Type... **Differences**
D0 (Difference|H0 = CV1.0 - CV2)................. **-0.2**
D1 (Difference|H1 = CV1.1 - CV2)................. **-0.15 -0.1 -0.05 0**
CV2 (Group 2 Coef of Variation)................... **0.4**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Hypotheses: H0: CV1 - CV2 = D0 vs. H1: CV1 - CV2 ≠ D0 (Two-Sided)

Power		Sample Size			Measurements	Coefficient of Variation			Difference		
					per Subject	H0 (Null)	H1 (Actual)	Reference	H0 (Null)	H1 (Actual)	
Target	Actual	N1	N2	N	M	CV1.0	CV1.1	CV2	D0	D1	Alpha
0.9	0.9002	358	358	716	2	0.2	0.25	0.4	-0.2	-0.15	0.05
0.9	0.9026	102	102	204	2	0.2	0.30	0.4	-0.2	-0.10	0.05
0.9	0.9003	52	52	104	2	0.2	0.35	0.4	-0.2	-0.05	0.05
0.9	0.9043	35	35	70	2	0.2	0.40	0.4	-0.2	0.00	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 from group 1. Each subject is measured M times.
N2 The number of subjects from group 2. Each subject is measured M times.
N The total number of subjects. N = N1 + N2.
M The number of measurements per subject.
CV1.0 The within-subject coefficient of variation in group 1 assumed by H0.
CV1.1 The within-subject coefficient of variation in group 1 at which the power is calculated. That is, it is the value of CV1 assumed by H1.
CV2 The within-subject coefficient of variation in group 2 assumed by both H0 and H1.
D0 The difference between CV1.0 and CV2 assumed by H0. D0 = CV1.0 - CV2.
D1 The difference between CV1.1 and CV2 at which the power is calculated (assumed by H1). D1 = CV1.1 - CV2.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design with replicates will be used to test whether the difference in within-subject coefficients of variation is different from -0.2 (H0: CV1 - CV2 = -0.2 versus H1: CV1 - CV2 ≠ -0.2, CVi = $\sigma i / \mu i$). Each subject will be measured 2 times. The comparison will be made using a two-sided, two-sample Z-test with a Type I error rate (α) of 0.05. To detect a within-subject coefficient of variation difference of -0.15 (CV1 = 0.25, CV2 = 0.4) with 90% power, the number of subjects needed will be 358 in Group 1, and 358 in Group 2.

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%	358	358	716	448	448	896	90	90	180
20%	102	102	204	128	128	256	26	26	52
20%	52	52	104	65	65	130	13	13	26
20%	35	35	70	44	44	88	9	9	18

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, 448 subjects should be enrolled in Group 1, and 448 in Group 2, to obtain final group sample sizes of 358 and 358, respectively.

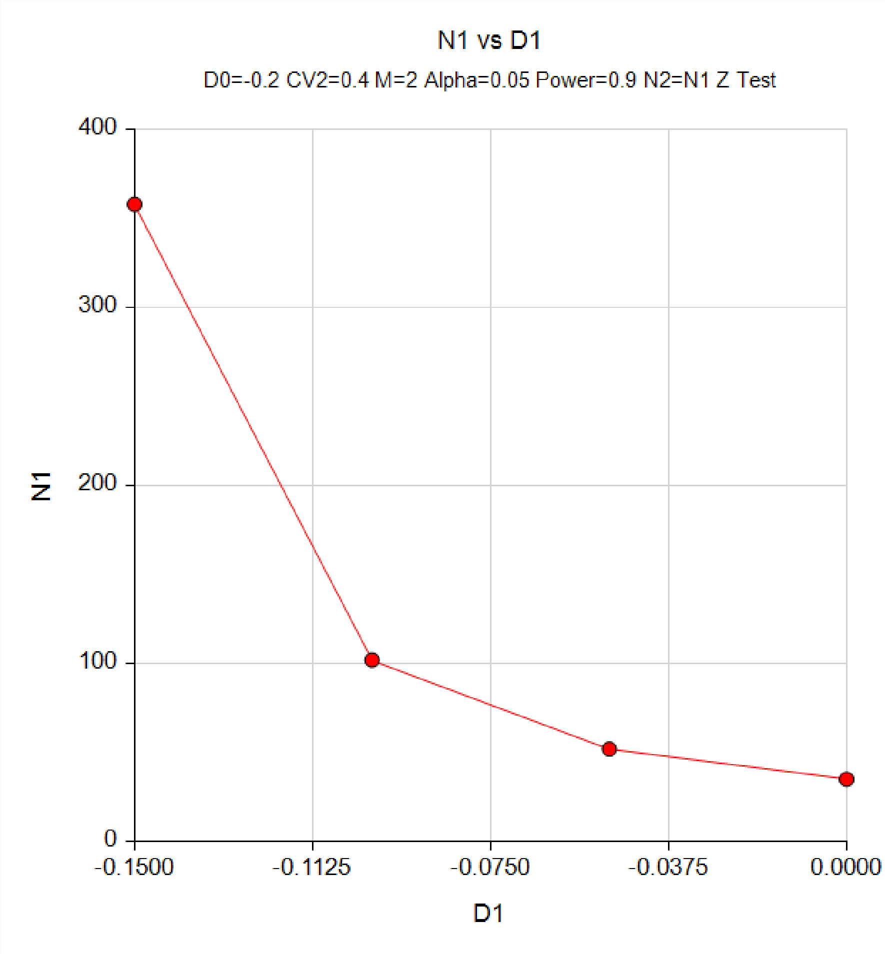
References

Quan, H. and Shih, W.J. 1996. 'Assessing reproducibility by the within-subject coefficient of variation with random effects models'. Biometrics, 52, pages 1195-1203.
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.

This report gives the sample sizes for the indicated scenarios.

Plots Section

Plots



This plot shows the relationship between sample size and D1.

Example 2 – Validation using Chow et al. (2018)

Chow *et al.* (2018) pages 203-204 presents an example of a one-sided, lower-tail test in which CV1.1 = 0.5, CV1.0 = 0.8, CV2 = 0.7, M = 2, alpha = 0.05, and power = 0.8. The sample size is found to be 34 per group.

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: CV1-CV2 < D0)**
Power.. **0.80**
Alpha.. **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **2**
Input Type... **Coefficients of Variation**
CV1.0 (Group 1 Coef of Variation|H0) **0.8**
CV1.1 (Group 1 Coef of Variation|H1) **0.5**
CV2 (Group 2 Coef of Variation).................... **0.7**

Output

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

Numeric Results

Solve For: Sample Size
Hypotheses: H0: CV1 - CV2 ≥ D0 vs. H1: CV1 - CV2 < D0 (One-Sided)

Power		Sample Size				Coefficient of Variation			Difference		
Target	Actual	N1	N2	N	Measurements per Subject M	H0 (Null) CV1.0	H1 (Actual) CV1.1	Reference CV2	H0 (Null) D0	H1 (Actual) D1	Alpha
0.8	0.8052	34	34	68	2	0.8	0.5	0.7	0.1	-0.2	0.05

The sample sizes match Chow et al. (2018).