Chapter 145

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 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 (2014) and 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

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

$$H_0: CV_1 - CV_2 = 0 \quad \text{versus} \quad H_1: CV_1 - CV_2 \neq 0.$$

The test statistic used to test this hypothesis is

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

where

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

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 combination of tests is given by

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

where

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

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

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, and the value of CV2 to 1.2. They want to compute the necessary sample size when the alternative CV1 is between 0.5 and 1.0. 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**
Power... **0.90**
Alpha.. **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **2**
Input Type... **Coefficient of Variation**
CV1 (Group 1 Coef of Variation|H1) **0.5 0.6 0.7 0.8 0.9 1.0**
CV2 (Group 2 Coef of Variation)................... **1.2**

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 = 0 vs. H1: CV1 - CV2 ≠ 0

Power		Sample Size			Measurements per Subject	Coefficient of Variation		Difference	
Target	Actual	N1	N2	N	M	CV1	CV2	D1	Alpha
0.9	0.9007	55	55	110	2	0.5	1.2	-0.7	0.05
0.9	0.9020	78	78	156	2	0.6	1.2	-0.6	0.05
0.9	0.9011	118	118	236	2	0.7	1.2	-0.5	0.05
0.9	0.9011	198	198	396	2	0.8	1.2	-0.4	0.05
0.9	0.9005	385	385	770	2	0.9	1.2	-0.3	0.05
0.9	0.9001	968	968	1936	2	1.0	1.2	-0.2	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 times each subject is measured.
CV1 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.
D1 The difference between CV1 and CV2 at which the power is calculated. D1 = CV1 - 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 there is a difference in within-subject coefficients of variation (H0: CV1 = CV2 versus H1: CV1 ≠ CV2, CVi = σi / μi). 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 -0.7 (CV1 = 0.5, CV2 = 1.2) with 90% power, the number of subjects needed will be 55 in Group 1, and 55 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%	55	55	110	69	69	138	14	14	28
20%	78	78	156	98	98	196	20	20	40
20%	118	118	236	148	148	296	30	30	60
20%	198	198	396	248	248	496	50	50	100
20%	385	385	770	482	482	964	97	97	194
20%	968	968	1936	1210	1210	2420	242	242	484

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, 69 subjects should be enrolled in Group 1, and 69 in Group 2, to obtain final group sample sizes of 55 and 55, respectively.

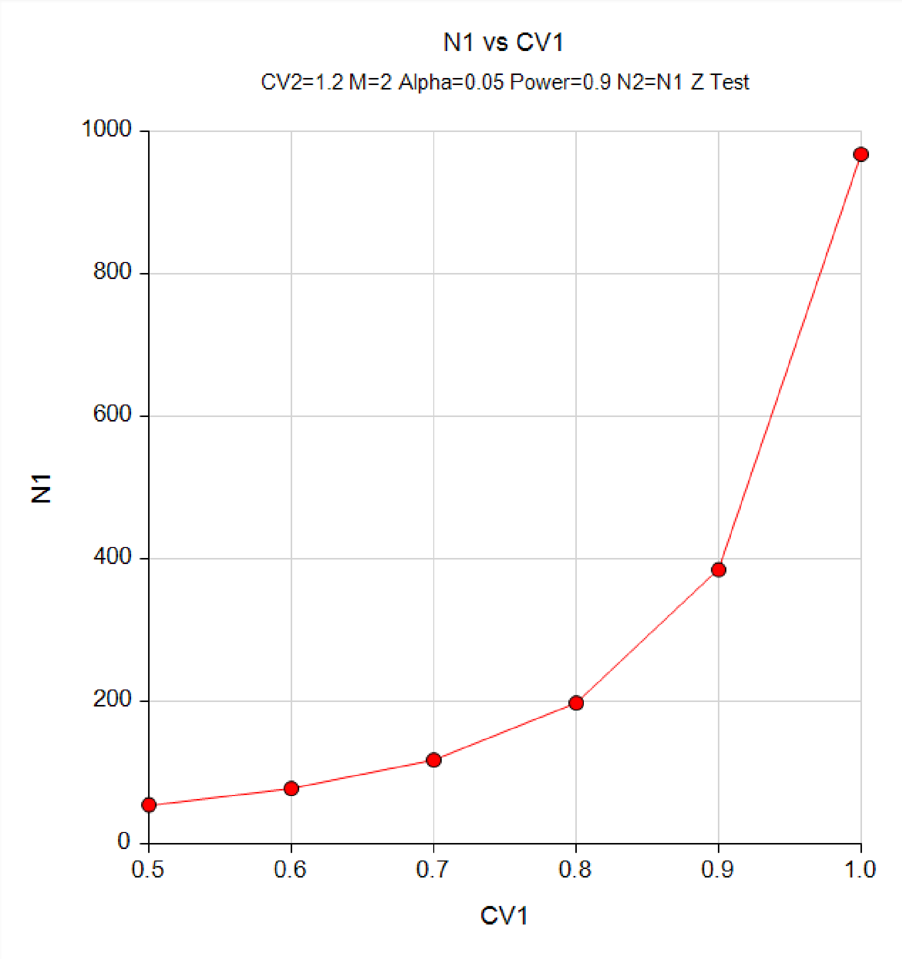
References

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. 2014. Biosimilars Design and Analysis of Follow-on Biologics, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
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 CV1.

Example 2 – Validation using Hand Calculations

We could not find a worked example in the literature, so we will validate this procedure using hand calculations applied to the following sample size formula given on page 202 of Chow *et al.* (2018).

$$N_1 = N_2 = \frac{\left(\sigma_1^{*2} + \sigma_2^{*2}\right)\left(z_{\alpha/2} + z_\beta\right)^2}{(CV_1 - CV_2)^2}$$

Now, using some of the results of Example 9.2.1.4 on page 203, we have CV1 = 0.5, CV2 = 0.7, significance level = 0.05, power = 0.8, and M = 2. On page 204, we are shown that $\sigma_1^{*2} = 0.125$ and $\sigma_2^{*2} = 0.363$. Hence, the above formula becomes

$$N_1 = N_2 = \frac{(0.125 + 0.363)(-1.96 - 0.8416)^2}{(0.5 - 0.7)^2}$$

This reduces to N_1 = 95.8.

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**
Group Allocation	**Equal (N1 = N2)**
M (Measurements Per Subject)	**2**
Input Type	**Coefficient of Variation**
CV1 (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 = 0 vs. H1: CV1 - CV2 ≠ 0

Power		Sample Size			Measurements per Subject	Coefficient of Variation			
Target	Actual	N1	N2	N	M	CV1	CV2	Difference D1	Alpha
0.8	0.8013	96	96	192	2	0.5	0.7	-0.2	0.05

The sample size matches the hand-calculated result.