Chapter 148

Superiority by a Margin Tests for the Difference of Two Within-Subject CV's in a Parallel Design

Introduction

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

The following hypotheses are usually used to test for the superiority by a margin of CV

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

Note that *D*0 is assumed to be negative since smaller CVs are 'better'.

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 its within-subject CV is superior by a margin to a reference 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 0.5, D0 to 0.4, and D1 to -0.30 -0.25 -0.20 -0.15. 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	**Differences**
D0 (Superiority Difference)	**-0.1**
D1 (Actual Difference)	**-0.30 -0.25 -0.20 -0.15**
CV2 (Group 2 Coef of Variation)	**0.5**

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 where D0 < 0 (One-Sided)

Power		Sample Size			Measurements per Subject	Coefficient of Variation			Difference		
Target	Actual	N1	N2	N	M	Superiority CV1.0	Actual CV1.1	Reference CV2	Superiority D0	Actual D1	Alpha
0.9	0.9064	30	30	60	2	0.4	0.20	0.5	-0.1	-0.30	0.05
0.9	0.9045	56	56	112	2	0.4	0.25	0.5	-0.1	-0.25	0.05
0.9	0.9014	134	134	268	2	0.4	0.30	0.5	-0.1	-0.20	0.05
0.9	0.9002	585	585	1170	2	0.4	0.35	0.5	-0.1	-0.15	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 superiority boundary. CVs below this value are concluded as superior.
CV1.1 The actual CV of group 1 at which the power is calculated (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 superiority difference (CV1.0 - CV2). D0 = CV1.0 - CV2.
D1 The actual difference (CV1.1 - 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 Group 1 coefficient of variation (σ1 / μ1) is superior to the Group 2 coefficient of variation (σ2 / μ2) by a margin, by testing whether the difference in within-subject coefficients of variation is less than -0.1 (H0: CV1 - CV2 ≥ -0.1 versus H1: CV1 - CV2 < -0.1). Each subject will be measured 2 times. The comparison will be made using a one-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 -0.3 (CV1 = 0.2, CV2 = 0.5) with 90% power, the number of subjects needed will be 30 in Group 1, and 30 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%	30	30	60	38	38	76	8	8	16
20%	56	56	112	70	70	140	14	14	28
20%	134	134	268	168	168	336	34	34	68
20%	585	585	1170	732	732	1464	147	147	294

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, 38 subjects should be enrolled in Group 1, and 38 in Group 2, to obtain final group sample sizes of 30 and 30, respectively.

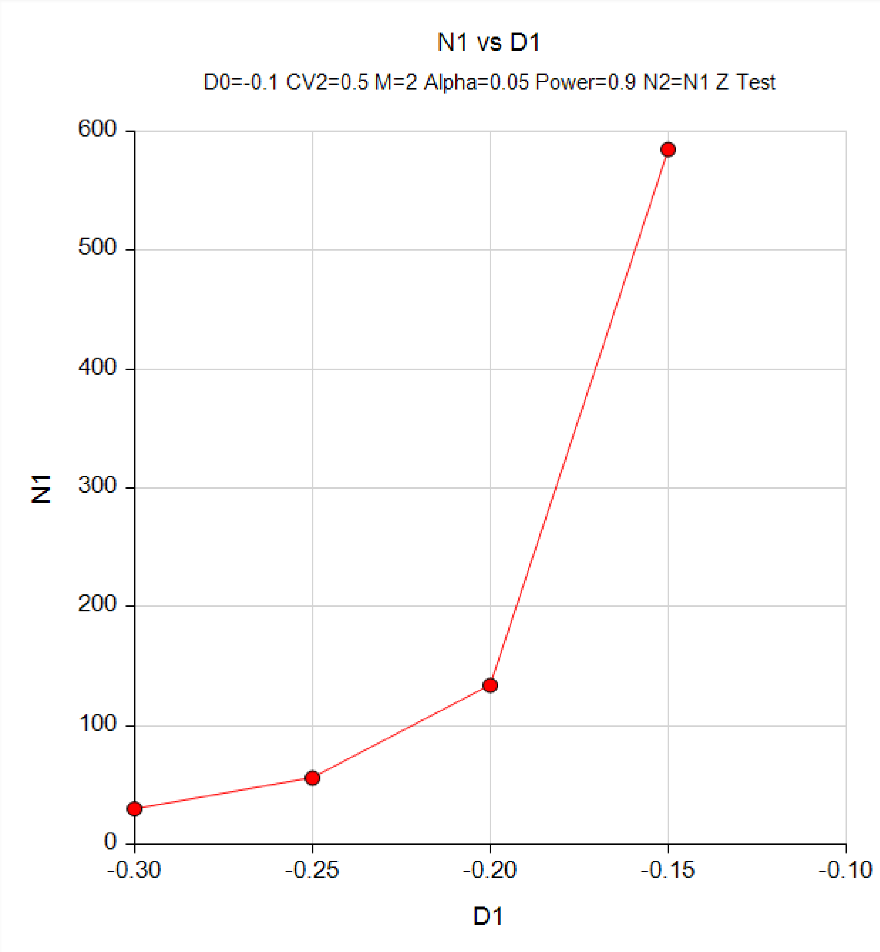
References

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 Hand Calculations

We could not find a validation example in the literature, so we will validate this procedure with an example calculated by hand using the formulas given earlier.

Suppose CV1.1 = 0.5, CV1.0 = 0.6, CV2 = 0.7, M = 2, alpha = 0.05, and N1 = N2 = 302. This leads to $\sigma_1^{*2} = 0.125$ and $\sigma_2^{*2} = 0.3626$.

The power calculations proceed as follows

$$\mu_z = \frac{(CV_1 - CV_2) - D0}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}} = \frac{(0.5 - 0.7) - (-0.1)}{\sqrt{\frac{0.125}{302} + \frac{0.3626}{302}}} = \frac{-0.1}{0.0401817} = -2.4886947$$

Hence

$$\text{Power} = \Phi(z_\alpha - \mu_z) = \Phi(-1.6448536 + 2.4886947) = 0.8006.$$

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	**Power**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**302**
M (Measurements Per Subject)	**2**
Input Type	**Coefficients of Variation**
CV1.0 (Superiority Coef of Variation)	**0.6**
CV1.1 (Actual Coef of Variation)	**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: Power
Hypotheses: H0: CV1 - CV2 ≥ D0 vs. H1: CV1 - CV2 < D0 where D0 < 0 (One-Sided)

	Sample Size			Measurements	Coefficient of Variation					
								Difference		
				per Subject	Superiority	Actual	Reference	Superiority	Actual	
Power	N1	N2	N	M	CV1.0	CV1.1	CV2	D0	D1	Alpha
0.8006	302	302	604	2	0.6	0.5	0.7	-0.1	-0.2	0.05

The power matches the hand calculations.