Chapter 149

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

Introduction

This procedure calculates power and sample size of equivalence tests for the difference of within-subject coefficients of variation (CV) from a parallel design with replicates (repeated measurements) of a particular treatment. These tests are based on the TOST methodology. 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.

Biosimilarity

Two treatments are said to be biosimilar if both their means and their variances are equivalent. The equivalence of their variances may be established by comparing their coefficients of variation.

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

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

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

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

where

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

Testing Equivalence

The following hypotheses are usually used to test for the equivalence of two group CVs

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

The two one-sided test statistics used to test this hypothesis is

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

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 of non-equivalence is rejected if $T_- < z_\alpha$ or $T_+ > z_{1-\alpha}$.

Power

The power of this combination of tests is given by (see Julious (2010) page 15)

$$\text{Power} = \text{Power}_1 + \text{Power}_2 - 1$$

where

$$\text{Power}_1 = \Phi(\mu_{z1} - z_\alpha)$$

$$\text{Power}_2 = \Phi(\mu_{z2} - z_\alpha)$$

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

and

$$\mu_{z1} = \frac{|(CV_2 - CV_1) - D0|}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}}$$

$$\mu_{z2} = \frac{|(CV_2 - CV_1) + D0|}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}}$$

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 non-inferior 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 0.4, D0 to 0.2, and D1 to -0.1 -0.05 0 0.05 0.1. 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.. **0.9**
Alpha... **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **2**
D0 (Equivalence) **0.2**
D1 (Actual Difference).................................... **-0.1 -0.05 0 0.05 0.1**
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
TOST Hypotheses: H0: |CV1 - CV2| ≥ D0 vs. H1: |CV1 - CV2| < D0

Power		Sample Size			Measurements	Coefficient of Variation					
						Equivalence Limits			Difference		
Target	Actual	N1	N2	N	per Subject M	Lower CV1.L	Upper CV1.U	Reference CV2	Equivalence D0	Actual D1	Alpha
0.9	0.9019	83	83	166	2	0.2	0.6	0.4	0.2	-0.10	0.05
0.9	0.9034	43	43	86	2	0.2	0.6	0.4	0.2	-0.05	0.05
0.9	0.9047	36	36	72	2	0.2	0.6	0.4	0.2	0.00	0.05
0.9	0.9001	60	60	120	2	0.2	0.6	0.4	0.2	0.05	0.05
0.9	0.9012	164	164	328	2	0.2	0.6	0.4	0.2	0.10	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.L	The lower equivalence boundary. CVs between CV1.L and CV1.U are considered equivalent (similar).
CV1.U	The upper equivalence boundary. CVs between CV1.L and CV1.U are considered equivalent (similar).
CV2	The within-subject coefficient of variation in group 2 assumed by both H0 and H1.
D0	The equivalence margin |CV1 - CV2|.
D1	The actual difference (CV1 - CV2) at which the power is calculated (assumed by H1).
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 equivalent to the Group 2 coefficient of variation (σ2 / μ2), by testing whether the difference in within-subject coefficients of variation is between -0.2 and 0.2 (H0: CV1 - CV2 ≤ -0.2 or CV1 - CV2 ≥ 0.2 versus H1: -0.2 < CV1 - CV2 < 0.2). Each subject will be measured 2 times. The comparison will be made using two one-sided, two-sample Z-tests with an overall Type I error rate (α) of 0.05. To detect a within-subject coefficient of variation difference of -0.1 (CV1 = 0.3, CV2 = 0.4) with 90% power, the number of subjects needed will be 83 in Group 1, and 83 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%	83	83	166	104	104	208	21	21	42
20%	43	43	86	54	54	108	11	11	22
20%	36	36	72	45	45	90	9	9	18
20%	60	60	120	75	75	150	15	15	30
20%	164	164	328	205	205	410	41	41	82

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, 104 subjects should be enrolled in Group 1, and 104 in Group 2, to obtain final group sample sizes of 83 and 83, respectively.

References

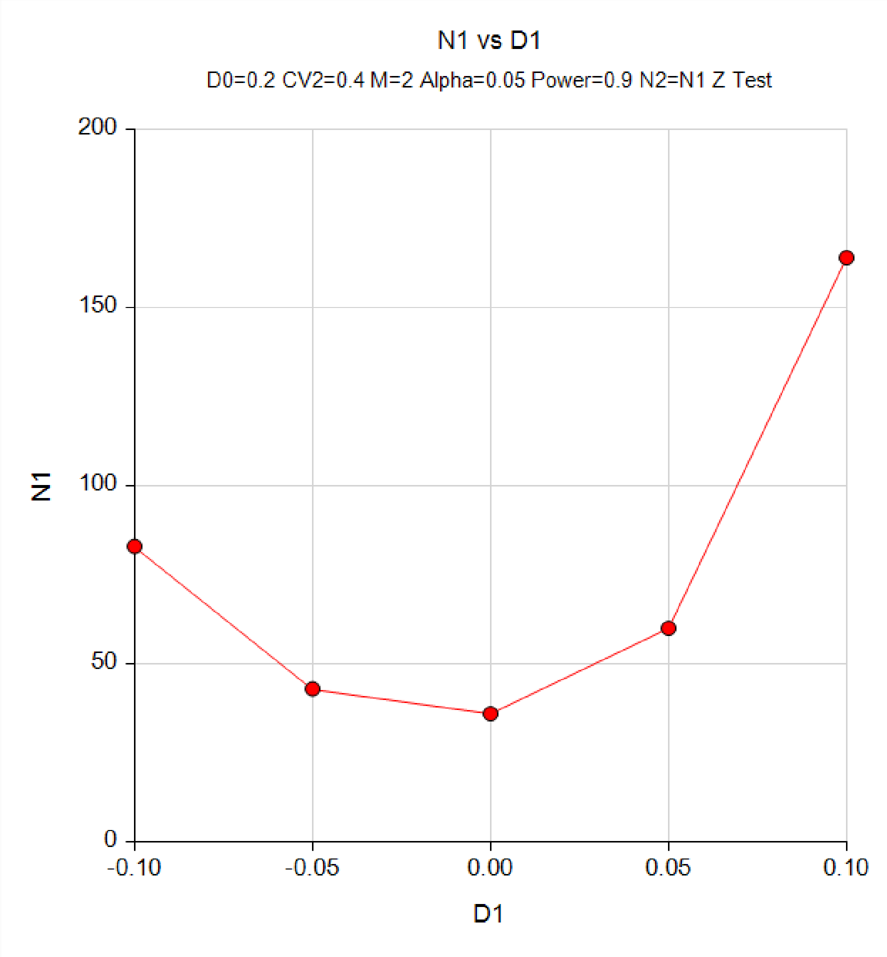
Quan, H. and Shih, W.J. 1996. 'Assessing reproducibility by the within-subject coefficient of variation with random effects models'. Biometrics, 52, pages 1195-1203.
Chow, S.C. 2014. Biosimilars Design and Analysis of Follow-on Biologics, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Chow, 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.

Note that the required sample sizes are not symmetric about D1 = 0. This is because the variances are based on D1 and so they are different depending on whether D1 > 0 and D1 < 0. For example, if D1 = 0.1, the value of CV1 used to calculate the power will be 0.5. However, if D1 = -0.1, the value of CV1 used to calculate the power will be 0.3. Since the power equations use CV1 in the computation of the variance, these two values of D1 will result in different power values.

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 present calculations by hand. Chow *et al.* (2018) page 203 presents the following formula for the direct calculation of sample size

$$N1 = N2 = \frac{\left(z_{1-\alpha} + z_{1-\frac{\beta}{2}}\right)^2 (\sigma_1^{*2} + \sigma_2^{*2})}{(D0 - |CV_1 - CV_2|)^2}$$

Suppose CV2 = 0.7, D0 = 0.2, D1 = 0, M = 2, alpha = 0.05, and power = 0.9. The sample size is found to be

$$N1 = N2 = \frac{(1.645 + 1.645)^2 (0.3626 + 0.3626)}{(0.2 - |0|)^2} = 196.2 \approx 197.$$

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... **0.9**
Alpha.. **0.05**
Group Allocation .... **Equal (N1 = N2)**
M (Measurements Per Subject) **2**
D0 (Equivalence) **0.2**
D1 (Actual Difference)................................... **0**
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
TOST Hypotheses: H0: |CV1 - CV2| ≥ D0 vs. H1: |CV1 - CV2| < D0

						Coefficient of Variation					
						Equivalence Limits			Difference		
Power		Sample Size			Measurements per Subject						
Target	Actual	N1	N2	N	M	Lower CV1.L	Upper CV1.U	Reference CV2	Equivalence D0	Actual D1	Alpha
0.9	0.9014	197	197	394	2	0.5	0.9	0.7	0.2	0	0.05

The sample size matches the hand calculations.