

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 ($j = 1, \dots, N_i$), and k th measurement ($k = 1, \dots, M$). The simple one-way random mixed effects model leads to the following estimates of CV1 and CV2

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

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

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

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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

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

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

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

where $D0$ 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

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

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

where $\Phi(x)$ 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.

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains the parameters associated with this test such as sample sizes, alpha, and power.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. Under most situations, you will select either *Power* or *Sample Size*.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of non-equivalent CVs when in fact the CVs are equivalent.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Values must be between zero and one. Often, a value of 0.025 is used for one-sided tests (such as this).

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size (When Solving for Sample Size)

Group Allocation

Select the option that describes the constraints on *N1* or *N2* or both.

The options are

- **Equal ($N1 = N2$)**
This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.
- **Enter $N2$, solve for $N1$**
Select this option when you wish to fix *N2* at some value (or values), and then solve only for *N1*. Please note that for some values of *N2*, there may not be a value of *N1* that is large enough to obtain the desired power.

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- **Enter $R = N2/N1$, solve for $N1$ and $N2$**

For this choice, you set a value for the ratio of $N2$ to $N1$, and then PASS determines the needed $N1$ and $N2$, with this ratio, to obtain the desired power. An equivalent representation of the ratio, R , is

$$N2 = R * N1.$$

- **Enter percentage in Group 1, solve for $N1$ and $N2$**

For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed $N1$ and $N2$ with this percentage to obtain the desired power.

$N2$ (Sample Size, Group 2)

This option is displayed if Group Allocation = "Enter $N2$, solve for $N1$ "

$N2$ is the number of items or individuals sampled from the Group 2 population.

$N2$ must be ≥ 2 . You can enter a single value or a series of values.

R (Group Sample Size Ratio)

This option is displayed only if Group Allocation = "Enter $R = N2/N1$, solve for $N1$ and $N2$."

R is the ratio of $N2$ to $N1$. That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of $N2$ to $N1$ while solving for $N1$ and $N2$. Only sample size combinations with this ratio are considered.

$N2$ is related to $N1$ by the formula:

$$N2 = [R \times N1],$$

where the value $[Y]$ is the next integer $\geq Y$.

For example, setting $R = 2.0$ results in a Group 2 sample size that is double the sample size in Group 1 (e.g., $N1 = 10$ and $N2 = 20$, or $N1 = 50$ and $N2 = 100$).

R must be greater than 0. If $R < 1$, then $N2$ will be less than $N1$; if $R > 1$, then $N2$ will be greater than $N1$. You can enter a single or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for $N1$ and $N2$."

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for $N1$ and $N2$. Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

Sample Size (When Not Solving for Sample Size)

Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal ($N1 = N2$)**

This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.

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- **Enter N1 and N2 individually**

This choice permits you to enter different values for $N1$ and $N2$.

- **Enter N1 and R, where $N2 = R * N1$**

Choose this option to specify a value (or values) for $N1$, and obtain $N2$ as a ratio (multiple) of $N1$.

- **Enter total sample size and percentage in Group 1**

Choose this option to specify a value (or values) for the total sample size (N), obtain $N1$ as a percentage of N , and then $N2$ as $N - N1$.

Sample Size Per Group

This option is displayed only if Group Allocation = "Equal ($N1 = N2$)."

The Sample Size Per Group is the number of items or individuals sampled. Since the sample sizes are the same in each group, this value is the value for $N1$, and also the value for $N2$.

The Sample Size Per Group must be ≥ 2 . You can enter a single value or a series of values.

N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = "Enter N1 and N2 individually" or "Enter N1 and R, where $N2 = R * N1$."*

$N1$ is the number of items or individuals sampled from the Group 1 population.

$N1$ must be ≥ 2 . You can enter a single value or a series of values.

N2 (Sample Size, Group 2)

This option is displayed only if Group Allocation = "Enter N1 and N2 individually."

$N2$ is the number of items or individuals sampled from the Group 2 population.

$N2$ must be ≥ 2 . You can enter a single value or a series of values.

R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter N1 and R, where $N2 = R * N1$."*

R is the ratio of $N2$ to $N1$. That is,

$$R = N2/N1$$

Use this value to obtain $N2$ as a multiple (or proportion) of $N1$.

$N2$ is calculated from $N1$ using the formula:

$$N2 = [R \times N1],$$

where the value $[Y]$ is the next integer $\geq Y$.

For example, setting $R = 2.0$ results in a Group 2 sample size that is double the sample size in Group 1.

R must be greater than 0. If $R < 1$, then $N2$ will be less than $N1$; if $R > 1$, then $N2$ will be greater than $N1$. You can enter a single value or a series of values.

Total Sample Size (N)

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines $N1$ and $N2$.

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 4. You can enter a single value or a series of values.

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Percent in Group 1

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

M (Measurements Per Subject)

Enter one or more values for M: the number of repeated measurements made on each subject.

You can enter a single value such as 2, a series of values such as 2 3 4, or 2 to 8 by 1.

The range is $M \geq 2$.

Effect Size (CV = Coefficient of Variation)

D0 (Equivalence Difference)

Enter one or more values for D0. D0 is sometimes called the *Margin of Equivalence*. It is the largest distance above or below CV2 which will still result in the conclusion of equivalence. As long as the absolute difference is between these two values, the difference is not large enough to be of practical importance.

CV (coefficient of variation) is the within-subject standard deviation divided by the mean.

The range of D0 is $D0 > 0$.

Syntax

You can enter a single value such as 0.3, a list of values such as 0.1 0.2 0.3, or a range of values such as 0.2 to 0.9 BY 0.1.

D1 (Actual Difference)

Enter one or more values for the actual difference (CV1-CV2). Hence, this is the difference at which the power is calculated.

CV (coefficient of variation) is the within-subject standard deviation divided by the mean.

D1 is in the same scale as D0 and CV2.

D1 can be any number, positive, negative, or zero. Usually, D1 is between $-D0$ and $D0$.

You can enter a single value such as 0.3, a list of values such as 0.0 0.1 0.2 0.3, or a range of values such as 0.0 to 0.9 BY 0.1.

CV2 (Group 2 Coef of Variation)

Enter one or more values for within-subject coefficient of variation (CV2) in group 2. It is used to define CV2 for both H0 and H1.

CV is the within-subject standard deviation divided by the mean.

Although, strictly speaking, CVs can be negative since means can be negative, we assume that CVs are positive (> 0).

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

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Difference of Two Within-Subject CV's in a Parallel Design** procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
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

Annotated Output

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

Numeric Results

TOST Hypotheses: $H_0: |CV1 - CV2| \geq D_0$ vs. $H_1: |CV1 - CV2| < D_0$

Actual Power	Grp 1 Sample Size N1	Grp 2 Sample Size N2	N	Meas Per Subj M	Grp 2 CV CV2	Lower Equiv Bndry CV1.L	Upper Equiv Bndry CV1.U	Equiv Margin D0	Actual Diff D1	Alpha
0.9019	83	83	166	2	0.400	0.200	0.600	0.200	-0.100	0.050
0.9034	43	43	86	2	0.400	0.200	0.600	0.200	-0.050	0.050
0.9047	36	36	72	2	0.400	0.200	0.600	0.200	0.000	0.050
0.9001	60	60	120	2	0.400	0.200	0.600	0.200	0.050	0.050
0.9012	164	164	328	2	0.400	0.200	0.600	0.200	0.100	0.050

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.

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Report Definitions

TOST Hypotheses: $H_0: |CV1 - CV2| \geq D_0$ vs. $H_1: |CV1 - CV2| < D_0$

Power is the probability of rejecting a false null hypothesis.

N_1 is the number of subjects from group 1. Each subject is measured M times.

N_2 is the number of subjects from group 2. Each subject is measured M times.

N is the total number of subjects. $N = N_1 + N_2$.

M is the number of measurements per subject.

CV_2 is the within-subject coefficient of variation in group 2 assumed by both H_0 and H_1 .

$CV_{1.L}$ is the lower equivalence boundary. CVs between $CV_{1.L}$ and $CV_{1.U}$ are considered equivalent (similar).

$CV_{1.U}$ is the upper equivalence boundary. CVs between $CV_{1.L}$ and $CV_{1.U}$ are considered equivalent (similar).

D_0 is the equivalence margin $|CV1 - CV2|$.

D_1 is the actual difference ($CV1 - CV2$) at which the power is calculated (assumed by H_1).

Alpha is the probability of rejecting a true null hypothesis, H_0 .

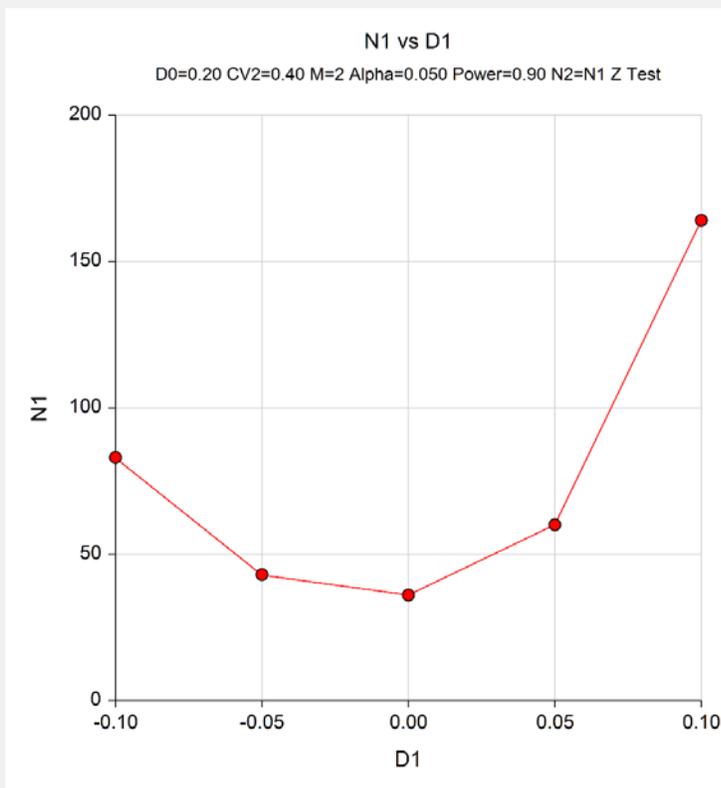
Summary Statements

A study is being conducted to test the equivalence (or similarity) of a particular group (group 1) compared to a reference group (group 2) with regards to their within-subject coefficients of variation (CVs). Group sample sizes of 83 and 83 achieve 90% power to reject the null hypothesis that the $|CV$ difference is greater than the equivalence limit of 0.200 at a significance level of 0.050. The TOST testing procedure is being used. The CV of group 2 is 0.400. The difference in CV at which the power is calculated is -0.100. Each subject is measured 2 times.

This report gives the sample sizes for the indicated scenarios.

Note that the required sample sizes are not symmetric about $D_1 = 0$. This is because the variances are based on D_1 and so they are different depending on whether $D_1 > 0$ and $D_1 < 0$. For example, if $D_1 = 0.1$, the value of CV_1 used to calculate the power will be 0.5. However, if $D_1 = -0.1$, the value of CV_1 used to calculate the power will be 0.3. Since the power equations use CV_1 in the computation of the variance, these two values of D_1 will result in different power values.

Plot Section



This plot shows the relationship between sample size and D_1 .

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Difference of Two Within-Subject CV's in a Parallel Design** procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
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										
TOST Hypotheses: H0: CV1 - CV2 ≥ D0 vs. H1: CV1 - CV2 < D0										
Actual Power	Grp 1 Sample Size N1	Grp 2 Sample Size N2	N	Meas Per Subj M	Grp 2 CV CV2	Lower Equiv Bndry CV1.L	Upper Equiv Bndry CV1.U	Equiv Margin D0	Actual Diff D1	Alpha
0.9014	197	197	394	2	0.700	0.500	0.900	0.200	0.000	0.050

The sample size matches the hand calculations.