

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 ($j = 1, \dots, N_i$), 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

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

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

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

where

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

Testing Inequality

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

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

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

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

where

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

and

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

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 equal CVs when in fact the CVs are unequal.

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. In this procedure, a type-I error occurs when you reject the null hypothesis of equal variances when in fact the variances are equal.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha for a two-sided test 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.

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

- **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.
- **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.

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

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.

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 (Number of Replicates)

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)

Input Type

Indicate what type of values to enter to specify the coefficients of variation (CV). Regardless of the entry type chosen, the test statistics used in the power and sample size calculations are the same. This option is simply given for convenience in specifying the CV.

The choices are

- **Coefficient of Variation**
Enter CV1 (Group 1 Coef of Variation|H1) and CV2 (Group 2 Coef of Variation).
- **Differences**
Enter D1 (Difference|H1 = CV1-CV2) and CV2 (Group 2 Coef of Variation).

Tests for the Difference of Two Within-Subject CV's in a Parallel Design**CV1 (Group 1 Coef of Variation|H1)**

Enter one or more values for within-subject coefficient of variation (CV1) in group 1 under H1. Hence, this is the value of CV1 at which the power is calculated.

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 > 0 .

D1 (Difference|H1 = CV1 – CV2)

Enter one or more values for difference between the within-subject coefficients of variation in group 1 and group 2 at which the power is calculated.

This difference is used to calculate CV1 for use in the power formula. The relationship is $D1 = CV1 - CV2$.

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

The value of D1 is restricted in that $D1 \neq 0$.

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).

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 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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **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.....	0.90
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

Annotated Output

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

Numeric Results

Actual Power	Group 1 Sample Size N1	Group 2 Sample Size N2	Measures Per Subject N	M	Group 1 Coef of Variation CV1	Group 2 Coef of Variation CV2	Diff CV1-CV2 D1	Alpha
0.9007	55	55	110	2	0.500	1.200	-0.700	0.050
0.9020	78	78	156	2	0.600	1.200	-0.600	0.050
0.9011	118	118	236	2	0.700	1.200	-0.500	0.050
0.9011	198	198	396	2	0.800	1.200	-0.400	0.050
0.9005	385	385	770	2	0.900	1.200	-0.300	0.050
0.9001	968	968	1936	2	1.000	1.200	-0.200	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.

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

Report Definitions

$H_0: D_1 = CV_1 - CV_2 = 0$. $H_1: D_1 = CV_1 - CV_2 \neq 0$.

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 times each subject is measured.

CV_1 is the within-subject coefficient of variation in group 1 at which the power is calculated. That is, it is the value of CV_1 assumed by H_1 .

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

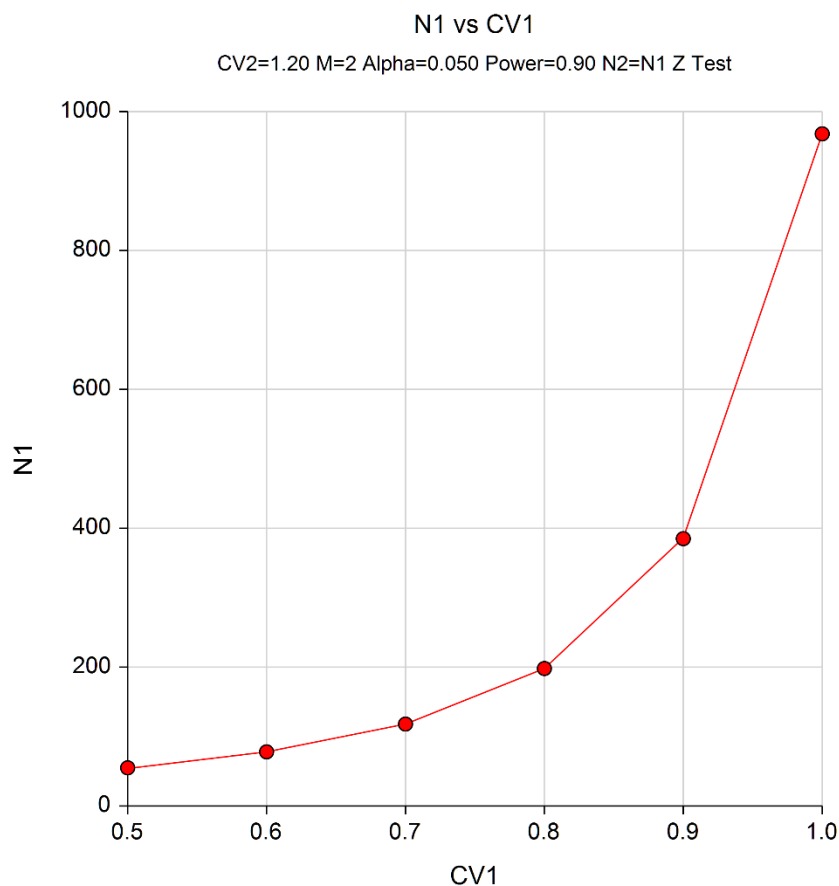
D_1 is the difference between CV_1 and CV_2 at which the power is calculated.

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

Summary Statements

A study is being conducted to test the inequality of the two group within-subject coefficients of variation. Group sample sizes of 55 and 55 achieve 90% power to reject the null hypothesis of equality at a significance level of 0.050. The coefficient of variation of group 1 assumed by the alternative hypothesis is 0.500. The coefficient of variation of group 2 is 1.200. Thus, the difference is -0.700. Each subject is measured 2 times.

This report gives the sample sizes for the indicated scenarios.

Plot Section

This plot shows the relationship between sample size and CV_1 .

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).

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

Now, using some of the results of Example 9.2.1.4 on page 203, we have $CV_1 = 0.5$, $CV_2 = 0.7$, 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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **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 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Power.....	0.80
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									
Actual	Group 1 Sample Size	Group 2 Sample Size	Measures Per Subject N	M	Group 1 Coef of Variation CV1	Group 2 Coef of Variation CV2	Diff CV1-CV2 D1	Alpha	
0.8013	96	96	192	2	0.500	0.700	-0.200	0.050	

The sample size matches the hand-calculated result.