Chapter 147

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

Introduction

This procedure calculates power and sample size of non-inferiority 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

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

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

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

where

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

Testing Non-Inferiority

The following hypotheses are usually used to test for the non-inferiority of CV

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

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

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

and

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

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 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.

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.

- **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 ≥ *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.

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 ≥ *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 (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 ≥ 2.

Effect Size (CV = Coefficient of Variation)

Input Type

Indicate the type of values to enter to specify the coefficients of variation (CV). Regardless of the input 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 CVs.

The choices are

- **Coefficients of Variation**

  Enter CV1.0 (Non-Inferiority Coef of Variation), CV1.1 (Actual Coef of Variation), and CV2 (Group 2 Coef of Variation)

- **Differences**

  Enter D0 (Non-Inferiority Difference), D1 (Actual Difference), and CV2 (Group 2 Coef of Variation)

CV1.0 (Non-Inferiority Coef of Variation)

Enter one or more values for the group 1 within-subject coefficient of variation (CV1.0) to be used as the non-inferiority boundary. If CV1 is greater than this amount, its non-inferiority cannot be concluded at the alpha and power that have been specified.

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.

Typically, 0 < CV2 < CV1.0.

CV1.0 is usually set slightly above the value of CV2. Their difference represents the non-inferiority margin.

CV1.1 (Actual Coef of Variation)

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

D0 (Non-Inferiority Difference)

Enter one or more values for D0, the maximum CV difference (CV1 - CV2) which will still result in the conclusion that group 1's CV is not inferior to group 2's CV, even though CV1 > CV2. This is often referred to as the non-inferiority margin.

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

Statistical Hypotheses

(Assumes smaller CVs are better)

H0: C1 - C2 ≥ D0 or H0: C1 ≥ C2 + D0

H1: C1 - C2 < D0 or H1: C1 < C2 + D0

where D0 > 0.

The range of D0 is given by 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.

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).

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, CV1.0 to 0.5, and CV1.1 to 0.2 0.3 0.4 0.45. 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 **Non-Inferiority 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	**0.90**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
M (Measurements Per Subject)	**2**
Input Type	**Differences**
D0 (Non-Inferiority Difference)	**0.1**
D1 (Actual Difference)	**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

One-Sided 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	Non-Inf CV1 Bndry CV1.0	Actual CV1 Value CV1.1	Grp 2 CV CV2	CV1.0 - CV2 D0	CV1.1 - CV2 D1	Alpha
0.9049	21	21	42	2	0.500	0.300	0.400	0.100	-0.100	0.050
0.9040	43	43	86	2	0.500	0.350	0.400	0.100	-0.050	0.050
0.9015	113	113	226	2	0.500	0.400	0.400	0.100	0.000	0.050
0.9002	539	539	1078	2	0.500	0.450	0.400	0.100	0.050	0.050

References

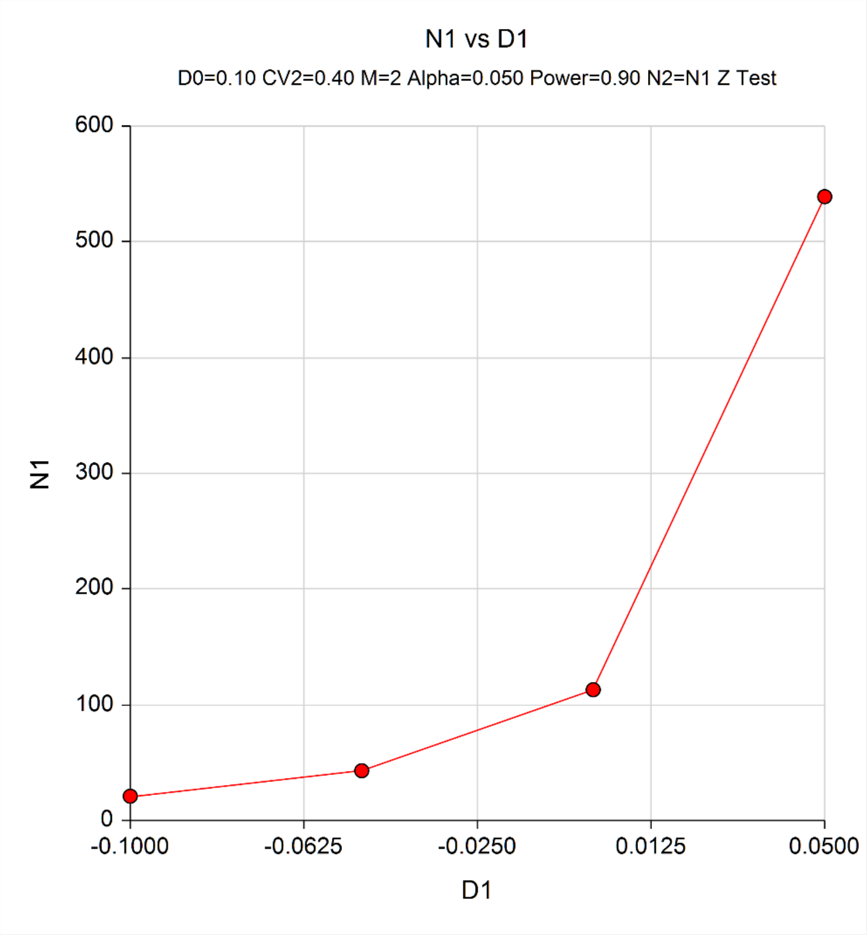
Quan, H. and Shih, W.J. 1996. 'Assessing reproducibility by the within-subject coefficient of variation with random effects models'. Biometrics, 52, pages 1195-1203.
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

Report Definitions
One-Sided Hypotheses: H0: CV1 - CV2 ≥ D0 vs. H1: CV1 - CV2 < D0
Power is the probability of rejecting a false null hypothesis.
N1 is the number of subjects from group 1. Each subject is measured M times.
N2 is the number of subjects from group 2. Each subject is measured M times.
N is the total number of subjects. N = N1 + N2.
M is the number of measurements per subject.
CV1.0 is the non-inferiority boundary. CVs below this value are concluded as non-inferior.
CV1.1 is the actual CV of group 1 at which the power is calculated (the value of CV1 assumed by H1).
CV2 is the within-subject coefficient of variation in group 2 assumed by both H0 and H1.
D0 is the non-inferiority difference (CV1.0 - CV2).
D1 is the actual difference (CV1.1 - CV2) at which the power is calculated (assumed by H1).
Alpha is the probability of rejecting a true null hypothesis, H0.

Summary Statements
A study is being conducted to test the non-inferiority 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 21 and 21 achieve 90% power to reject the null hypothesis that the CV difference is greater than or equal to the non-inferiority margin 0.100 at a significance level of 0.050. The non-inferiority boundary of the CV of group 1 is 0.500. The actual value of the CV of group 1 assumed by the alternative hypothesis is 0.300. 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.

Plot Section



This plot shows the relationship between sample size and D1.

Example 2 – Validation using Chow *et al.* (2018)

Chow *et al.* (2018) pages 203-204 presents an example of a one-sided, lower-tail test in which CV1.1 = 0.5, CV1.0 = 0.8, CV2 = 0.7, M = 2, alpha = 0.05, and power = 0.8. The sample size is found to be 34 per group.

Setup

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

Option	Value
Design Tab	
Solve For	**Sample Size**
Power	**0.80**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
M (Measurements Per Subject)	**2**
Input Type	**Coefficients of Variation**
CV1.0 (Non-Inferiority Coef of Variation)	**0.8**
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

One-Sided 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	Non-Inf CV1 Bndry CV1.0	Actual CV1 Value CV1.1	Grp 2 CV CV2	CV1.0 - CV2 D0	CV1.1 - CV2 D1	Alpha
0.8052	34	34	68	2	0.800	0.500	0.700	0.100	-0.200	0.050

The sample sizes match Chow et al. (2018).