

## Chapter 146

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

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### Introduction

This procedure calculates power and sample size of inequality tests with a non-zero null 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.

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### 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

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

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

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

where

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

## Testing Inequality (Two-Sided)

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

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

The two-sided test statistic used to test this hypothesis is

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

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 is rejected if  $T < z_{\alpha/2}$  or  $T > z_{1-\alpha/2}$ .

## Power

The power of this test 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

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

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.

## Testing Inequality (Upper One-Sided)

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

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

The one-sided test statistic used to test this hypothesis is

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

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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 is rejected if  $T > z_{1-\alpha}$ .

### Power

The power of this combination of tests is given by

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

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.

## Testing Inequality (Lower One-Sided)

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

$$H_0: (CV1 - CV2) \geq D0 \text{ versus } H_1: (CV1 - CV2) < D0.$$

The one-sided test statistic used to test this hypothesis is

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

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 is rejected if  $T < z_\alpha$ .

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### 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

$$\mu_z = \frac{(CV_1 - CV_2) - D_0}{\sqrt{\frac{\sigma_1^{*2}}{N_1} + \frac{\sigma_2^{*2}}{N_2}}}$$

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*.

### Test Direction

#### Alternative Hypothesis

Specify whether the alternative hypothesis of the test is one-sided or two-sided.

Note that this option impacts the value of alpha. The value of alpha is used directly for one-sided tests. For two-sided tests, alpha is replaced by alpha/2.

#### *Two-Sided Hypothesis Test*

H0: CV1-CV2 = D0 vs. H1: CV1-CV2 ≠ D0

#### *One-Sided Hypothesis Tests*

Lower: H0: CV1-CV2 ≥ D0 vs. H1: CV1-CV2 < D0

Upper: H0: CV1-CV2 ≤ D0 vs. H1: CV1-CV2 > D0

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## 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. Often, a value of 0.05 is used for two-sided tests and 0.025 is used for one-sided tests.

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

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## 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  $\geq 2$ . You can enter a single value or a series of values.

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### 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.

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## 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  $\geq 2$ . You can enter a single value or a series of values.

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### 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  $\geq 2$ . 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  $\geq 2$ . 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.

### 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  $M \geq 2$ .

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## 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

- **Coefficients of Variation**

Enter CV1.0 (Group 1 Coef of Variation|H0), CV1.1 (Group 1 Coef of Variation|H1), and CV2 (Group 2 Coef of Variation)

- **Differences**

Enter D0 (Difference|H0 = CV1.0-CV2), D1 (Difference|H1 = CV1.1-CV2), and CV2 (Group 2 Coef of Variation)

### CV1.0 (Group 1 Coef of Variation|H0)

Enter one or more values for within-subject coefficient of variation (CV1) in group 1 under H0. 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  $> 0$ .

### CV1.1 (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 non-zero null value of CV1.

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 (Difference|H0 = CV1 – CV2)

Enter one or more values for D0, the difference between the within-subject coefficients of variation in group 1 and group 2 under H0. Hence, this specifies a non-zero null for the difference.

This difference is used to calculate CV1 for use in the power formula. The relationship is  $D0 = CV1.0 - CV2$ .

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

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

### 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 ( $> 0$ ).

## 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, CV2 to 0.4, D0 to -0.2, and D1 to -0.15 or -0.1 or -0.05 or 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 **Non-Zero Null 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
<b>Design Tab</b>	
Solve For .....	Sample Size
Alternative Hypothesis .....	Two-Sided (H1: CV1-CV2 ≠ D0)
Power .....	0.90
Alpha .....	0.05
Group Allocation .....	Equal (N1 = N2)
M (Measurements Per Subject) .....	2
Input Type .....	Differences
D0 (Difference H0 = CV1.0 - CV2) .....	-0.2
D1 (Difference H1 = CV1.1 - CV2) .....	-0.15 -0.1 -0.05 0
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**

Two-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	Grp 1 CV H0 CV1.0	Grp 1 CV H1 CV1.1	Grp 2 CV CV2	CV1.0 - CV2 D0	CV1.1 - CV2 D1	Alpha
0.9002	358	358	716	2	0.200	0.250	0.400	-0.200	-0.150	0.050
0.9026	102	102	204	2	0.200	0.300	0.400	-0.200	-0.100	0.050
0.9003	52	52	104	2	0.200	0.350	0.400	-0.200	-0.050	0.050
0.9043	35	35	70	2	0.200	0.400	0.400	-0.200	0.000	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.

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

### Report Definitions

Two-Sided Hypotheses:  $H_0: CV_1 - CV_2 = D_0$  vs.  $H_1: CV_1 - CV_2 \neq D_0$

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.

$CV_{1.0}$  is the within-subject coefficient of variation in group 1 assumed by  $H_0$ .

$CV_{1.1}$  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  $H_1$ .

$D_0$  is the difference between  $CV_{1.0}$  and  $CV_2$  assumed by  $H_0$ .

$D_1$  is the difference between  $CV_{1.1}$  and  $CV_2$  at which the power is calculated (assumed by  $H_1$ ).

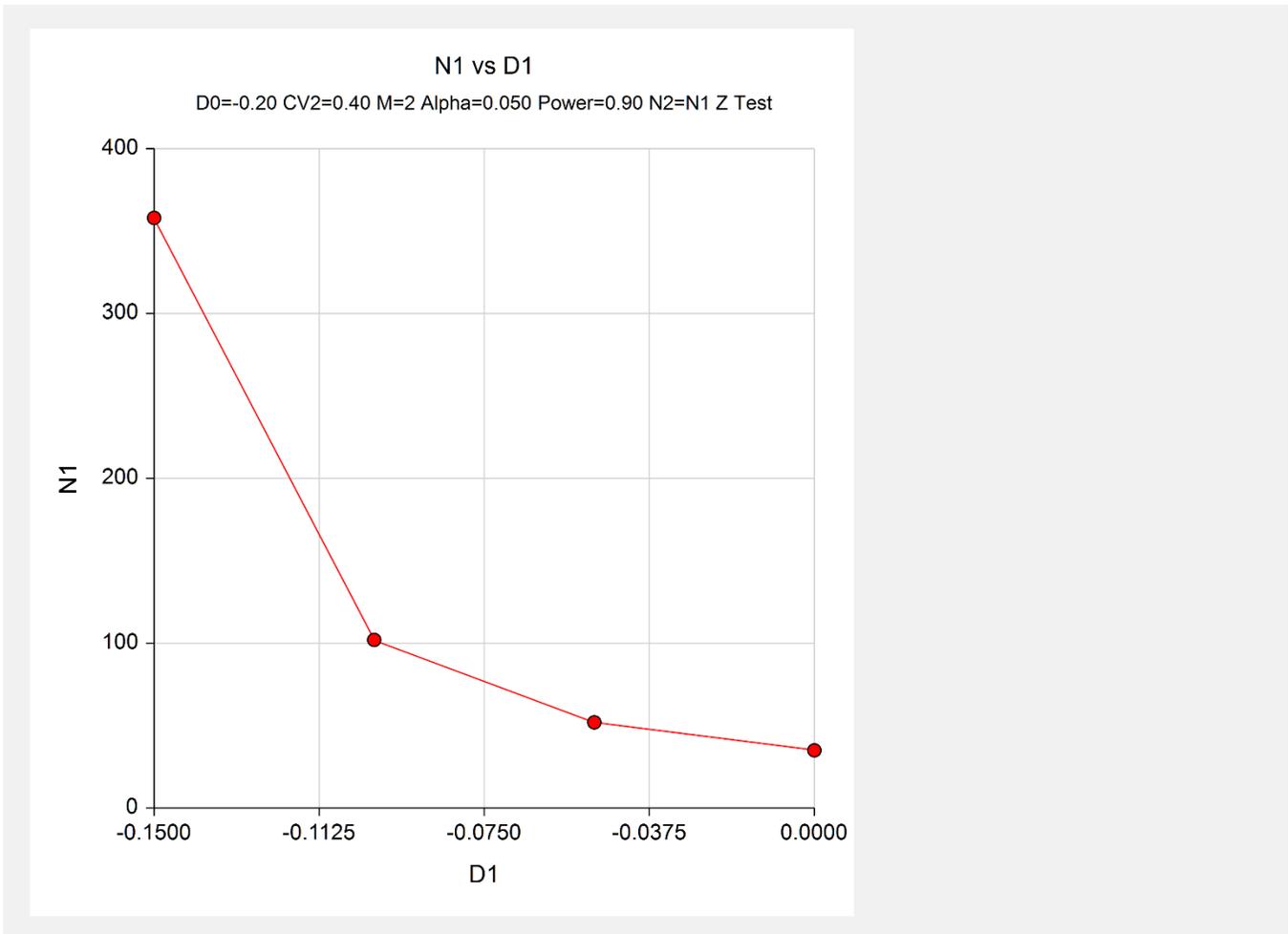
Alpha is the probability of rejecting a true null hypothesis,  $H_0$ .

### Summary Statements

A study is being conducted to test the inequality of two within-subject coefficients of variation (CVs). Group sample sizes of 358 and 358 achieve 90% power to reject the null hypothesis that the CV difference is -0.200 at a significance level of 0.050. The CV of group 1 used for the null hypothesis is 0.200. The CV of group 1 assumed by the alternative hypothesis is 0.250. The CV of group 2 is 0.400. The difference in CV at which the power is calculated is -0.150. 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  $D_1$ .

## 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  $CV_{1.1} = 0.5$ ,  $CV_{1.0} = 0.8$ ,  $CV_2 = 0.7$ ,  $M = 2$ ,  $\alpha = 0.05$ , and  $\text{power} = 0.8$ . 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-Zero Null 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>
<b>Design Tab</b>	
Solve For .....	Sample Size
Alternative Hypothesis .....	One-Sided (H1: $CV_1 - CV_2 < D_0$ )
Power .....	0.80
Alpha .....	0.05
Group Allocation .....	Equal ( $N_1 = N_2$ )
M (Measurements Per Subject) .....	2
Input Type .....	Coefficients of Variation
CV1.0 (Group 1 Coef of Variation H0) ....	0.8
CV1.1 (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										
One-Sided Hypotheses: $H_0: CV_1 - CV_2 \geq D_0$ vs. $H_1: CV_1 - CV_2 < D_0$										
Actual	Grp 1 Sample Size	Grp 2 Sample Size	N	Meas Per Subj M	Grp 1 CV H0 CV1.0	Grp 1 CV H1 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).