

## Chapter 491

# Tests for the Matched-Pair Difference of Two Means in a Cluster-Randomized Design

---

## Introduction

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are sampled, rather than individual subjects. This sample size and power procedure is used for the case where the subject responses are continuous (mean outcome). To reduce the variation (and thus increase power), clusters are matched, with one cluster of each pair assigned to the control group, and the other assigned the treatment group. This procedure gives the number of pairs needed for the desired power requirement.

The formulas used here are based on Hayes and Bennett (1999) and Hayes and Moulton (2009). The methods are discussed in Donner and Klar (2000) and briefly in Campbell and Walters (2014).

---

## Technical Details

---

### Definition of Terms

The following table presents the various terms that are used.

Group	1 (Control)	2 (Treatment)	
Sample size:	$K$	$K$	
Means:	$\mu_1$	$\mu_2$	
Standard Deviations:	$\sigma_1$	$\sigma_2$	(these are the within-cluster standard deviations)

Coefficient of Variation:  $CV_M$  (within-pair coefficient of variation between clusters in the absence of intervention)

Number of cluster pairs:  $K$  ( $2K$  is the total number of clusters)

Cluster size:  $M$  (Average number of individuals per cluster)

## Hypotheses

The null and alternative hypotheses are

$$H_0: \mu_{Diff} = 0 \quad \text{vs.} \quad H_1: \mu_{Diff} \neq 0$$

Corresponding one-sided hypotheses may also be used. These hypotheses may be tested based on an appropriate paired difference test.

## Sample Size and Power Calculations

### Sample Size Calculation

The sample size calculation for the number of cluster pairs, as given in Hayes and Bennett (1999) and Hayes and Moulton (2009), is

$$K = 2 + (z_{\alpha/2} + z_{\beta})^2 \frac{(\sigma_1^2 + \sigma_2^2)/M + CV_M^2(\mu_1^2 + \mu_2^2)}{(\mu_1 - \mu_2)^2}$$

### Estimating $CV_M$

Hayes and Bennett (1999) suggest that  $CV_M$  may be estimated based on the following, if prior data is available:

Let  $\mu_{ij}$  represent the true mean in the  $j^{\text{th}}$  cluster ( $j = 1, 2$ ) of the  $i^{\text{th}}$  pair ( $i = 1, \dots, M$ ) and  $\bar{x}_{ij}$  represent the corresponding observed mean. If the empirical variance of the  $i^{\text{th}}$  pair is called  $s_i^2$  then define

$$s_m^2 = \sum s_i^2 / M$$

as the average of the within-pair variances.

$CV_M$  may be estimated from

$$CV_M^2 = \frac{s_m^2 - Av(\hat{\sigma}_i^2/n_{ij})}{Av(\bar{x}_i^2)}$$

where  $n_{ij}$  is the number of individuals in the  $i^{\text{th}}$  pair of the  $j^{\text{th}}$  cluster, and  $Av()$  indicates the mean over all  $M$  clusters.

According to Hayes and Bennett (1999), "If only unmatched data are available, a conservative approach is to use [the coefficient of variation (SD/Mean) between clusters within each group] as an upper limit for  $CV_M$ ."

If no data is available, a series of plausible values, usually between 0 and 0.5, should be considered.

### Power Calculation

The corresponding power calculation to the sample size calculation above is

$$Power = 1 - \Phi \left( \sqrt{\frac{(K-2)(\mu_1 - \mu_2)^2}{(\sigma_1^2 + \sigma_2^2)/M + CV_M^2(\mu_1^2 + \mu_2^2)}} - z_{\alpha/2} \right)$$

where  $z_x = \Phi(x)$  is the standard normal distribution function.

---

## 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 most of the parameters and options that you will be concerned with.

---

#### Solve For

##### Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *Power*, *K*, *M*, and  $\mu_2$ .

Under most situations, you will select either *Power* to calculate power or *K* to calculate the number of cluster pairs. Occasionally, you may want to fix the number of clusters and find the necessary cluster size.

The value selected here always appears as the vertical axis on the charts (when applicable).

When searching for *M*, some scenarios with small *K*'s are not feasible.

---

#### Test

##### Alternative Hypothesis

Specify whether the test is one-sided or two-sided. The one-sided option specifies a one-tailed test.

---

#### 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.

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 commonly used.

A single value may be entered 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. Usually, the 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*.

---

## Sample Size – Number of Clusters & Cluster Size

### K (Number of Cluster Pairs)

This is the number of cluster pairs. Each cluster pair consists of two clusters that are matched or paired based on one or more criteria. The total sample size is equal to the number of clusters times the cluster size. This value must be a positive number. You can enter a single value such as 20 or a series of values such as 10 20 30 or 10 to 30 by 5.

### M (Cluster Size)

This is the average number of individuals or items per cluster. This value must be a positive number that is at least 1. It can be a decimal (fractional) number such as 20.7. You can enter a single value such as 50 or a series of values such as 40 50 60 or 40 to 60 by 5.

---

## Effect Size – Means

### $\mu_1$ (Mean for Group 1)

Enter a value (or range of values) for the group 1 (control group) mean. You can enter a single value such as 14 or a series of values such as 5 6 7 or 5 to 7 by 0.5.

### Enter $\mu_2$ , Diff, or Ratio for Group 2

This option lets you indicate how  $\mu_2$  is entered. The options are

- **$\mu_2$  (Mean for Group 2)**  
Enter the value of  $\mu_2$  directly.
- **Diff (Difference Between Means)**  
Enter values for the difference between the means ( $\text{Diff} = \mu_2 - \mu_1$ ). The value of  $\mu_2$  is equal to  $\mu_1 + \text{Diff}$ .
- **Ratio (Ratio of Means)**  
Enter values for the ratio of the means ( $\text{Ratio} = \mu_2 / \mu_1$ ). The value of  $\mu_2$  is equal to  $\mu_1 * \text{Ratio}$ . Note that the hypothesis still concerns the difference. This is just a convenient way of specifying a value.

### $\mu_2$ (Mean for Group 2)

*This option is displayed only if Enter  $\mu_2$ , Diff, or Ratio for Group 2 = “ $\mu_2$  (Mean of Group 2).”*

Enter a value (or range of values) for the mean in group 2 (treatment group). The value must be different from  $\mu_1$ . You can enter a single value such as 14 or a series of values such as 5 6 7 or 5 to 7 by 0.5.

### Diff (Difference Between Means)

*This option is displayed only if Enter  $\mu_2$ , Diff, or Ratio for Group 2 = “Diff (Difference Between Means).”*

Enter values for the difference between the means ( $\text{Diff} = \mu_2 - \mu_1$ ). The value of  $\mu_2$  is equal to  $\mu_1 + \text{Diff}$ . The range is any positive or negative value other than 0 ( $\text{Diff} \neq 0$ ). You can enter a single value such as 5 or a series of values such as 5 6 7 or 5 to 7 by 5.

### Ratio (Ratio of Means)

*This option is displayed only if Enter  $\mu_2$ , Diff, or Ratio for Group 2 = “Ratio (Ratio of Means).”*

Enter values for the ratio of the means ( $\text{Ratio} = \mu_2 / \mu_1$ ) at which the power is to be calculated. The value of  $\mu_2$  is calculated using  $\mu_1 * \text{Ratio}$ . The range is  $\text{Ratio} > 0$ , and  $\text{Ratio} \neq 1$ . Typically, Ratio is between 0.5 and 2.0. You can enter a single value such as 1.15 or a series of values such as 1.05 1.10 1.15 1.20 or 1.05 to 1.20 by 0.05.

---

## Effect Size – Within-Cluster Standard Deviations

### $\sigma_1$ (Standard Deviation for Group 1)

Enter a value (or range of values) for the group 1 (control group) within cluster standard deviation. The value must be greater than zero. You can enter a single value such as 5 or a series of values such as 5 6 7 or 5 to 7 by 0.5.

### $\sigma_2$ (Standard Deviation for Group 2)

Enter a value (or range of values) for the group 2 (treatment group) within cluster standard deviation. The value must be greater than zero. You can enter a single value such as 5 or a series of values such as 5 6 7 or 5 to 7 by 0.5.

---

## Effect Size – Within-Pair Coefficient of Variation between Clusters

### CVM (Within-Pair Coefficient of Variation)

Enter a value or values for the within-pair coefficient of variation (SD/Mean) between clusters in the absence of intervention. See the documentation or references for suggestions for estimating CVM. If prior information is not available, Hayes and Bennett (1999) suggest that CVM is usually less than 0.25 and seldom greater than 0.50. You can enter a single value such as 0.15 or a series of values such as 0.05 0.10 0.15 0.20 or 0.05 to 0.30 by 0.05.

## Tests for the Matched-Pair Difference of Two Means in a Cluster-Randomized Design

## Example 1 – Calculating Sample Size

One difficulty in calculating sample size for a matched-pair difference of two means in a cluster-randomized design is obtaining a value for  $CV_M$ , the within-pair coefficient of variation between clusters. This example shows how to enter a range of values to determine the effect of  $CV_M$  on sample size. Suppose that a cluster randomized study is to be conducted in which the control mean is assumed to be  $\mu_1 = 8.4$ , and the treatment mean is  $\mu_2 = 7.1$ . The within-cluster standard deviation for both groups is assumed to be 2.8. Each cluster is assumed to have about 120 individuals. A range of values between 0.05 and 0.5 for  $CV_M$  will be examined. The desired power and alpha are 0.9 and 0.05, respectively. The test will be a two-sided test.

### 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 Matched-Pair Difference of Two Means in a Cluster-Randomized 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>
<b>Design Tab</b>	
Solve For .....	<b>K (Number of Cluster Pairs)</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power .....	<b>0.90</b>
Alpha .....	<b>0.05</b>
M (Cluster Size) .....	<b>120</b>
$\mu_1$ (Mean for Group 1) .....	<b>8.4</b>
Enter $\mu_2$ , Diff, or Ratio for Group 2 .....	<b><math>\mu_2</math> (Mean for Group 2)</b>
$\mu_2$ (Mean for Group 2) .....	<b>7.1</b>
$\sigma_1$ (Standard Deviation for Group 1) .....	<b>2.8</b>
$\sigma_2$ (Standard Deviation for Group 2) .....	<b>2.8</b>
CVM (Within-Pair Coefficient of Variation) .....	<b>0.05 to 0.50 by 0.05</b>

### Annotated Output

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

### Numeric Results

**Numeric Results for a Two-Sided Test of a Matched-Pair Mean Difference in a Cluster-Randomized Design**  
Group 1 = Control, Group 2 = Treatment

Power	Number of Cluster Pairs K	Total Number of Clusters 2K	Cluster Size M	Total Size N = 2KM	Mean Gr 1 $\mu_1$	Mean Gr 2 $\mu_2$	Mean Diff. $\mu_2 - \mu_1$	Mean Ratio $\mu_2 / \mu_1$	$\sigma_1$	$\sigma_2$	Coef. of Var. CVM	Two-Sided Alpha
0.9281	5	10	120	1200	8.4	7.1	-1.3	0.85	2.8	2.8	0.050	0.050
0.9205	11	22	120	2640	8.4	7.1	-1.3	0.85	2.8	2.8	0.100	0.050
0.9042	20	40	120	4800	8.4	7.1	-1.3	0.85	2.8	2.8	0.150	0.050
0.9009	33	66	120	7920	8.4	7.1	-1.3	0.85	2.8	2.8	0.200	0.050
0.9011	50	100	120	12000	8.4	7.1	-1.3	0.85	2.8	2.8	0.250	0.050
0.9020	71	142	120	17040	8.4	7.1	-1.3	0.85	2.8	2.8	0.300	0.050
0.9002	95	190	120	22800	8.4	7.1	-1.3	0.85	2.8	2.8	0.350	0.050
0.9020	124	248	120	29760	8.4	7.1	-1.3	0.85	2.8	2.8	0.400	0.050
0.9016	156	312	120	37440	8.4	7.1	-1.3	0.85	2.8	2.8	0.450	0.050
0.9002	191	382	120	45840	8.4	7.1	-1.3	0.85	2.8	2.8	0.500	0.050

## Tests for the Matched-Pair Difference of Two Means in a Cluster-Randomized Design

### References

- Hayes, R.J. and Bennett, S. 1999. 'Simple sample size calculation for cluster-randomized trials'. International Journal of Epidemiology. Vol 28, pages 319-326.
- Hayes, R.J. and Moulton, L.H. 2009. Cluster Randomised Trials. CRC Press. New York.
- Campbell, M.J. and Walters, S.J. 2014. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Wiley. New York.

### Report Definitions

Power is the probability of rejecting a false null hypothesis.

K represents the number of cluster pairs needed in the design.

2K is the total number of clusters in the design, 2 clusters per pair.

M is the average number of individuals or items in each cluster.

N is the total number of individuals or items in the design.  $N = 2KM$ .

$\mu_1$  is the mean for the control group.

$\mu_2$  is the mean for the treatment group.

$\mu_2 - \mu_1$  is the difference between the treatment mean and the control mean.

$\mu_2 / \mu_1$  is the ratio of the treatment mean to the control mean.

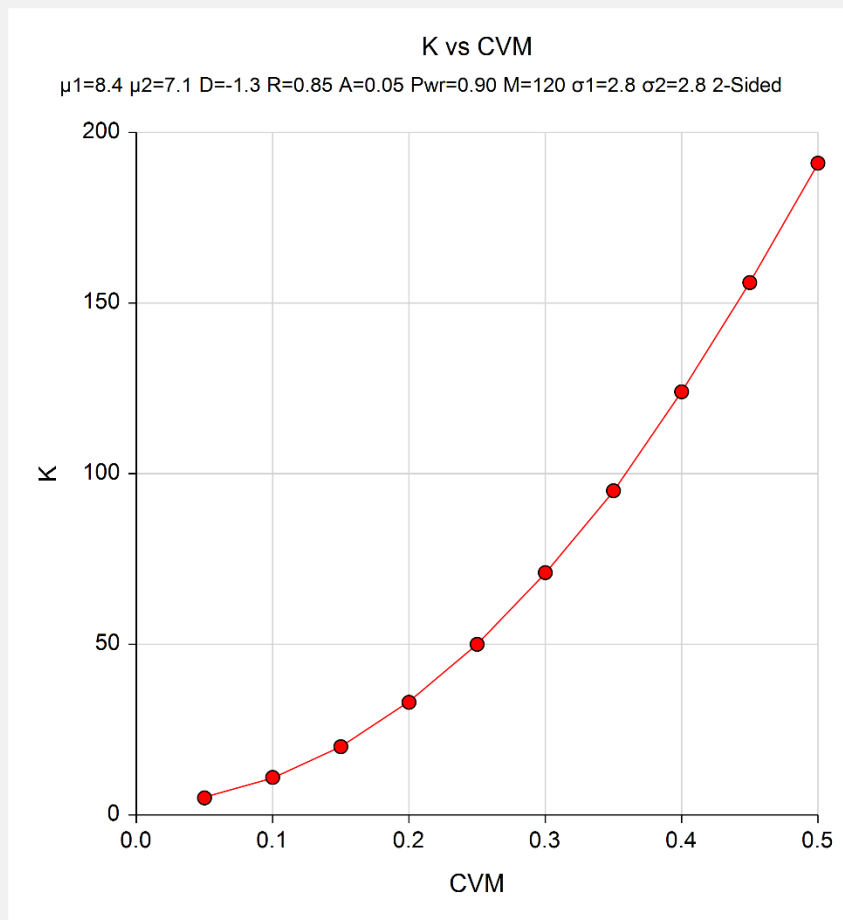
CVM is the within-pair coefficient of variation between clusters in the absence of intervention. See the documentation or references for suggestions for estimating CVM.

Alpha is the probability of rejecting a true null hypothesis, that is, rejecting  $H_0$  when the means are actually equal.

### Summary Statements

A sample of 5 cluster pairs (10 clusters) with 120 individuals per cluster achieves 93% power to detect a difference of -1.3 between the treatment mean 7.1 and the control mean 8.4. The within group standard deviation for group 1 is 2.8 and the within group standard deviation for group 2 is 2.8. The within-pair coefficient of variation between clusters is 0.050. A two-sided paired test of the mean difference is assumed, with a significance level of 0.050.

### Chart Section



This report shows the needed number of cluster pairs for each of the coefficient of variation values.

## Example 2 – Validation using Direct Calculation

Hayes and Bennett (1999) and Hayes and Moulton (2009) give formulas for sample size for tests of the matched-pair difference in a cluster-randomized design for comparing event rates, proportions, and means. However, the only example corresponds to the proportions case. Thus, we give an example where the number of cluster pairs needed is determined by direct calculation.

We will consider the (two-sided) case where  $\mu_1 = 4.5$ ;  $\mu_2 = 5.7$ ;  $\sigma_1 = 3.3$ ;  $\sigma_2 = 3.9$ ;  $M = 200$ ;  $\alpha = 0.05$ ;  $CVM = 0.25$ ;  $Power = 0.80$ .

$$\begin{aligned}
 K &= 2 + (z_{\alpha/2} + z_{\beta})^2 \frac{(\sigma_1^2 + \sigma_2^2)/M + CV_M^2(\mu_1^2 + \mu_2^2)}{(\mu_1 - \mu_2)^2} \\
 &= 2 + (1.9600 + 0.8416)^2 \frac{(3.3^2 + 3.9^2)/200 + 0.25^2(4.5^2 + 5.7^2)}{(4.5 - 5.7)^2} \\
 &= 2 + 7.84888 \frac{0.1305 + 0.0625(52.74)}{1.44} = 20.678
 \end{aligned}$$

## 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 Matched-Pair Difference of Two Means in a Cluster-Randomized 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 .....	<b>K (Number of Cluster Pairs)</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power .....	<b>0.80</b>
Alpha .....	<b>0.05</b>
M (Cluster Size) .....	<b>120</b>
$\mu_1$ (Mean for Group 1) .....	<b>4.5</b>
Enter $\mu_2$ , Diff, or Ratio for Group 2 .....	<b><math>\mu_2</math> (Mean for Group 2)</b>
$\mu_2$ (Mean for Group 2) .....	<b>5.7</b>
$\sigma_1$ (Standard Deviation for Group 1) .....	<b>3.3</b>
$\sigma_2$ (Standard Deviation for Group 2) .....	<b>3.9</b>
CVM (Within-Pair Coefficient of Variation) .....	<b>0.25</b>



## Tests for the Matched-Pair Difference of Two Means in a Cluster-Randomized Design

**Output**

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

**Numeric Results****Numeric Results for a Two-Sided Test of a Matched-Pair Mean Difference in a Cluster-Randomized Design**

Group 1 = Control, Group 2 = Treatment

	Number of Cluster Pairs	Total Number of Clusters	Cluster Size M	Total Size N = 2KM	Mean Gr 1 $\mu_1$	Mean Gr 2 $\mu_2$	Mean Diff. $\mu_2 - \mu_1$	Mean Ratio $\mu_2 / \mu_1$	$\sigma_1$	$\sigma_2$	Coef. of Var. CVM	Two- Sided Alpha
Power	K	2K	M	N = 2KM	$\mu_1$	$\mu_2$	$\mu_2 - \mu_1$	$\mu_2 / \mu_1$	$\sigma_1$	$\sigma_2$	CVM	Alpha
0.8067	21	42	200	8400	4.5	5.7	1.2	1.27	3.3	3.9	0.250	0.050

PASS calculates the number of cluster pairs needed to be 21, which matches the rounded-up calculation value.