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	μ_1	μ_2
Standard Deviations	σ_1	σ_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

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

Estimating CV_M

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

Let μ_{ij} represent the true mean in the j^{th} cluster (j = 1,2) of the i^{th} pair (i = 1, ..., M) and $\bar{x}_{ij}$ represent the corresponding observed mean. If the empirical variance of the i^{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^{th} pair of the j^{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.

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 μ1 = 8.4, and the treatment mean is μ2 = 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

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For .... **K (Number of Cluster Pairs)**
Alternative Hypothesis .... **Two-Sided**
Power.. **0.90**
Alpha... **0.05**
M (Cluster Size) **120**
μ1 (Mean for Group 1) **8.4**
Enter μ2, Diff, or Ratio for Group 2 .... **μ2 (Mean for Group 2)**
μ2 (Mean for Group 2) **7.1**
σ1 (Standard Deviation for Group 1).............. **2.8**
σ2 (Standard Deviation for Group 2).............. **2.8**
CVM (Within-Pair Coefficient of Variation)..... **0.05 to 0.50 by 0.05**

Output

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

Numeric Results

Solve For: K (Number of Cluster Pairs)
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Two-Sided

Power	Number of Cluster Pairs K	Total Number of Clusters 2K	Cluster Size M	Total Sample Size N	Mean Group 1 μ1	Mean Group 2 μ2	Mean Difference μ2 - μ1	Mean Ratio μ2 / μ1	Within-Cluster Standard Deviation Group 1 σ1	Within-Cluster Standard Deviation Group 2 σ2	Within-Pair Coefficient of Variation CVM	Alpha
0.9281	5	10	120	1200	8.4	7.1	-1.3	0.85	2.8	2.8	0.05	0.05
0.9205	11	22	120	2640	8.4	7.1	-1.3	0.85	2.8	2.8	0.10	0.05
0.9042	20	40	120	4800	8.4	7.1	-1.3	0.85	2.8	2.8	0.15	0.05
0.9009	33	66	120	7920	8.4	7.1	-1.3	0.85	2.8	2.8	0.20	0.05
0.9011	50	100	120	12000	8.4	7.1	-1.3	0.85	2.8	2.8	0.25	0.05
0.9020	71	142	120	17040	8.4	7.1	-1.3	0.85	2.8	2.8	0.30	0.05
0.9002	95	190	120	22800	8.4	7.1	-1.3	0.85	2.8	2.8	0.35	0.05
0.9020	124	248	120	29760	8.4	7.1	-1.3	0.85	2.8	2.8	0.40	0.05
0.9016	156	312	120	37440	8.4	7.1	-1.3	0.85	2.8	2.8	0.45	0.05
0.9002	191	382	120	45840	8.4	7.1	-1.3	0.85	2.8	2.8	0.50	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
K Represents the number of cluster pairs needed in the design.
2K The total number of clusters in the design, 2 clusters per pair.
M The average number of individuals or items in each cluster.
N The total number of individuals or items in the design. N = 2KM.
μ1 The mean for the control group.
μ2 The mean for the treatment group.
μ2 - μ1 The difference between the treatment mean and the control mean.
μ2 / μ1 The ratio of the treatment mean to the control mean.
σ1, σ2 The within-cluster standard deviations of groups 1 and 2, respectively.
CVM The within-pair coefficient of variation between clusters in the absence of intervention. See the documentation or references for suggestions for estimating CVM.
Alpha The probability of rejecting a true null hypothesis, that is, rejecting H0 when the means are actually equal.

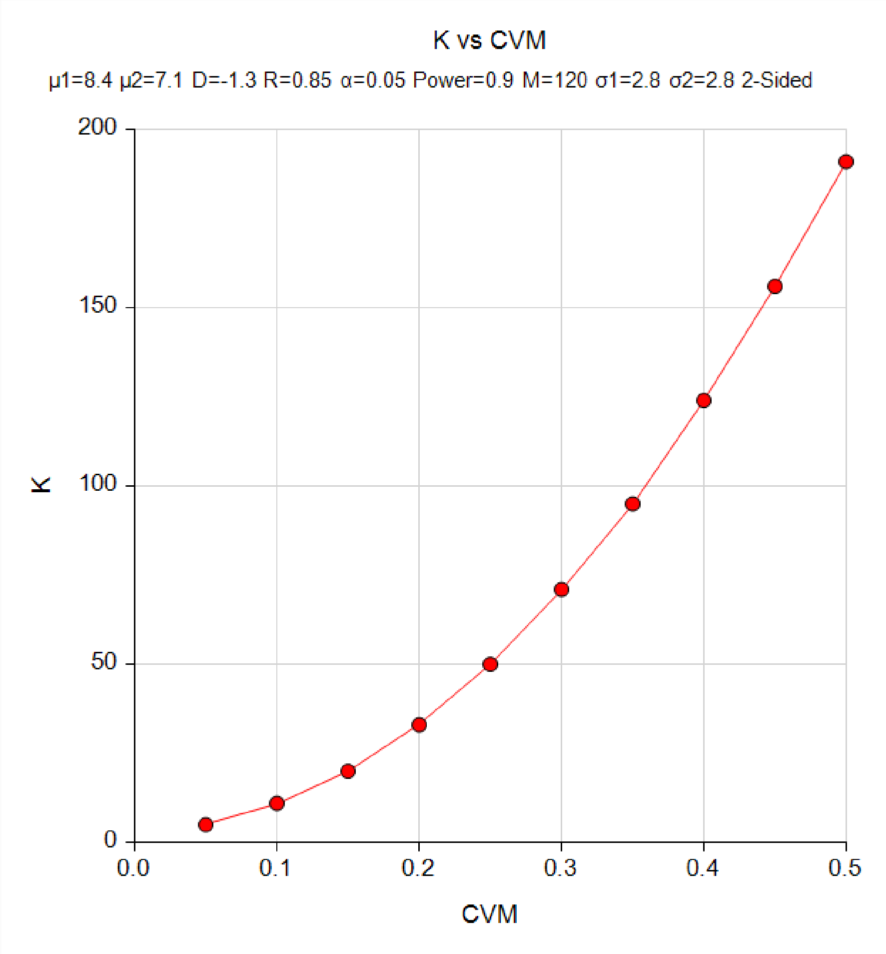
Summary Statements

A matched-cluster-pair cluster-randomized design will be used to test whether there is a difference in means (μ2 - μ1 = μtreatment - μcontrol). The comparison will be made using a two-sided, paired-difference Z-test, with a Type I error rate (α) of 0.05. The within-cluster standard deviation for Group 1 (control) is assumed to be 2.8 and the within-cluster standard deviation for Group 2 (treatment) is assumed to be 2.8. The within-pair coefficient of variation between clusters in the absence of intervention is assumed to be 0.05. To detect a mean difference of -1.3 (μ2 = 7.1, μ1 = 8.4) with 120 subjects per cluster and 90% power, the number of needed cluster pairs is 5, or 10 total clusters (1200 total subjects).

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.

Plots



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 *μ1* = 4.5; *μ2 = 5.7; σ1* = 3.3; *σ2 = 3.9; M = 200; alpha = 0.05; CVM = 0.25; Power = 0.80.*

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

$$= 2 + (1.9600 + 0.8416)^2 \frac{(3.3^2 + 3.9^2)/200 + 0.25^2(4.5^2 + 5.7^2)}{(4.5 - 5.7)^2}$$

$$= 2 + (7.84888)\left(\frac{0.1305 + 0.0625(52.74)}{1.44}\right)$$

$$= 20.678$$

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**K (Number of Cluster Pairs)**
Alternative Hypothesis	**Two-Sided**
Power	**0.80**
Alpha	**0.05**
M (Cluster Size)	**200**
μ1 (Mean for Group 1)	**4.5**
Enter μ2, Diff, or Ratio for Group 2	**μ2 (Mean for Group 2)**
μ2 (Mean for Group 2)	**5.7**
σ1 (Standard Deviation for Group 1)	**3.3**
σ2 (Standard Deviation for Group 2)	**3.9**
CVM (Within-Pair Coefficient of Variation)	**0.25**

Output

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

Numeric Results

Solve For: K (Number of Cluster Pairs)
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Two-Sided

					Mean				Within-Cluster Standard Deviation			
Power	Number of Cluster Pairs K	Total Number of Clusters 2K	Cluster Size M	Total Sample Size N	Group 1 μ1	Group 2 μ2	Difference μ2 - μ1	Ratio μ2 / μ1	Group 1 σ1	Group 2 σ2	Within-Pair Coefficient of Variation CVM	Alpha
0.8067	21	42	200	8400	4.5	5.7	1.2	1.27	3.3	3.9	0.25	0.05

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