

## Chapter 152

# Tests for Two Means in a Cluster-Randomized Design with Clustering in Only One Arm

## Introduction

This procedure computes power and sample size for a test comparing two means in cluster-randomized designs in which the outcome is a continuous normal random variable and clustering occurs in only one arm.

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are put into the treatment group or the control group. In this case, the means of the two arms (groups), where the first arm is made up of  $K_i$  clusters of  $M_{ij}$  individuals each and the second arm is made up of individuals, are to be tested using a modified z test.

For example, one arm might receive individual intervention (such as medicine) while the other receives this medicine plus some type of group therapy session. The fact that they attend this therapy session implies that they are “clustered”. The clustering occurs in only one arm.

## Technical Details

Our formulation comes from Moerbeek and Wong (2008). They combine two mixed models: one for the arm made up of individuals and a second, more, complicated model for the arm which accounts for the clustering. This type of design is also mentioned by Julious (2023).

The model for the second (non-clustered) arm is

$$y_i = \beta_0 + x_i' \beta + r_i$$

where  $y_i$  is a continuous outcome,  $x_i$  is a vector of covariates for subject  $i$ ,  $\beta$  is a vector of effects of these covariates, and  $r_i$  is a random error term with expectation zero and variance  $\sigma_r^2$ .

The mixed model for the first (clustered) arm is

$$y_{ij} = \beta_0 + \delta + x_{ij}' \beta + u_i + e_{ij}$$

where  $y_{ij}$  is a continuous outcome for subject  $i = 1, \dots, m_j$  within cluster  $j = 1, \dots, k$ ,  $\delta$  is the treatment effect to be tested,  $u_i$  is a random error term for clusters with expectation zero and variance  $\sigma_u^2$ , and  $e_{ij}$  is a random error term for subjects within a cluster with expectation zero and variance  $\sigma_e^2$ .

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Note that the variance of  $y_{ij}$  is  $\sigma_u^2 + \sigma_e^2$ . The intraclass correlation (ICC) is

$$\rho = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_e^2}.$$

These models can be combined into a single mixed model using

$$y_{ij} = \beta_0 + I_{ij}\delta + x'_{ij}\beta + I_{ij}u_i + e_{ij}$$

where  $I_{ij}$  is an indicator variable which is equal to one for subjects in the cluster arm and zero for subjects in the other, non-clustered, arm. Note that subjects in the non-clustered arm are assigned to a single "cluster"  $j = k + 1$ . Here  $k$  is the number of clusters in clustered arm. Note that  $\sigma_r^2 \neq \sigma_u^2 + \sigma_e^2$ , so the model is heteroscedastic (has unequal variances).

In this model, the treatment effect is measured by the difference in the two group means

$$\hat{\delta} = \bar{y}_1 - \bar{y}_2$$

The variance of this estimator is

$$\text{var}(\hat{\delta}) = \frac{\bar{m}\sigma_u^2 + \sigma_e^2}{\bar{m}k} + \frac{\sigma_r^2}{N_1} = \sigma_r^2 \left( \theta \frac{(\bar{m} - 1)\rho + 1}{\bar{m}k} + \frac{1}{N_2} \right)$$

where  $\bar{m}$  is the average cluster size,  $N_2$  is the number of subjects in the non-clustered arm, and

$$\theta = \frac{\sigma_u^2 + \sigma_e^2}{\sigma_r^2}.$$

Using the above, a large sample formula for computing the power of a two-sided test of the significance of the treatment effect at significance level  $\alpha$  is given by

$$\text{var}(\hat{\delta}) = \left( \frac{\delta}{z_{1-\frac{\alpha}{2}} + z_{\text{Power}}} \right)^2$$

For sample size calculation, we assume that the cluster sizes  $m_j$  are distributed with a mean cluster size of  $\bar{m}$  and a coefficient of variation of cluster sizes of  $COV$ . The accuracy of the variance of the two group means,  $\bar{Y}_i$ , can be enhanced by replacing  $\bar{m}$  in the numerator of the first term of  $\text{var}(\hat{\delta})$  with  $\bar{m}(COV^2 + 1)$ . See Julious (2023) page 86.

Assume that  $\delta = \mu_1 - \mu_2$  is to be tested using a t-test (small sample) or z-test (large sample). The statistical hypotheses are  $H_0: \delta = 0$  vs.  $H_a: \delta \neq 0$ . The test statistic

$$t = \frac{\bar{Y}_1 - \bar{Y}_2}{\sqrt{\text{var}(\hat{\delta})}}$$

has an approximate t distribution with degrees of freedom  $DF = N_2 + K_1\bar{m} - 2$  for a *subject-level* analysis.

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Let the noncentrality parameter  $\Delta = \delta / \sqrt{\text{var}(\hat{\delta})}$ . We can define the two critical values based on a central t-distribution with DF degrees of freedom as follows.

$$X_1 = t_{\frac{\alpha}{2}, DF}$$

$$X_2 = t_{1-\frac{\alpha}{2}, DF}$$

The power can be found from the following to probabilities

$$P_1 = H_{X_1, DF, \Delta}$$

$$P_2 = H_{X_2, DF, \Delta}$$

$$\text{Power} = 1 - (P_2 - P_1)$$

where  $H_{X, DF, \Delta}$  is the cumulative probability distribution of the noncentral-t distribution.

The power of a one-sided test can be calculated similarly.

Note that Julious (2023) uses a homoscedastic model that gives the same power values as these when  $\theta = 1$ . Candlish *et al.* (2018) recommend that the more complicated heteroscedastic model be used because of their findings in a large simulation study.

## Example 1 – Calculating Sample Size

Suppose that a cluster randomized study is to be conducted in which one arm (group 2) will receive an individual medical intervention while the other arm (group 1) receives this medicine plus a special group therapy session conducted by a trained therapist. These therapy sessions will be treated as clusters. Here, group 2 (the non-clustered subjects) is the 'control group' and group 1 (the clustered subjects) is the treatment group. The therapy sessions will involve 10 patients with a COV of cluster size of 0.65.

At the time of the design of the trial, little is known about the variances, so the study will be powered in terms of standardized values. This is accomplished the setting  $\sigma_2 = 1$  and defining  $\delta_s = \delta/\sigma_2$ .

The parameter values are set as follows:  $\alpha = 0.05$ ,  $power = 0.9$ ,  $R = 1.5$ ,  $\delta = 0.5$ ,  $\sigma_2 = 1$ ,  $\theta = 0.9, 1.0, 1.1$ ,  $\rho = 0.4$ ,  $M1 = 10$ , and  $COV = 0.65$ . Power is to be calculated for 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 .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>Two-Sided (Ha: <math>\delta \neq 0</math>, <math>\delta = \mu_1 - \mu_2</math>)</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter R = (K1 × M1) / N2, solve for K1 and N2</b>
R (Allocation Ratio) .....	<b>1.5</b>
M1 (Average Cluster Size).....	<b>10</b>
COV (Coefficient of Variation of Cluster Sizes).....	<b>0.65</b>
$\delta$ (Mean Difference = $\mu_1 - \mu_2$ ).....	<b>0.5</b>
$\sigma_2$ (Standard Deviation in Group 2) .....	<b>1</b>
$\Theta$ (Group Variance Ratio = $\sigma_1^2 / \sigma_2^2$ ) .....	<b>0.9 1 1.1</b>
$\rho$ (Intracluster Correlation, ICC) .....	<b>0.4</b>

## Output

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

## Numeric Reports

### Numeric Results

Solve For: Sample Size  
 Clustering: Group 1 has Clustering, Group 2 has No Clustering  
 Group Allocation: Enter R = (K1 × M1) / N2, solve for K1 and N2  
 Hypotheses: H0:  $\delta = 0$  vs. Ha:  $\delta \neq 0$

#### Group 1 Clusters

Power	Number of Clusters K1	Average Cluster Size M1	Coefficient of Variation of Cluster Sizes COV	Sample Size			Allocation Ratio R	Mean Difference $\delta$	Group Variance Ratio		Standard Deviation			Alpha
				N1	N2	N			ICC $\rho$	Between $\sigma_u$	Within $\sigma_e$	Group 2 $\sigma_2$		
0.90502	30	10	0.65	300	200	500	1.5	0.5	0.9	0.4	0.60000	0.73485	1	0.05
0.90819	33	10	0.65	330	220	550	1.5	0.5	1.0	0.4	0.63246	0.77460	1	0.05
0.90327	35	10	0.65	350	234	584	1.5	0.5	1.1	0.4	0.66332	0.81240	1	0.05

- Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
- K1 The number of clusters in group 1.
- M1 The average cluster size (number of subjects) of the clusters in group 1.
- COV The coefficient of variation of the cluster sizes. This is the standard deviation of cluster sizes divided by the average cluster size.
- N1, N2, and N The number of subjects in groups 1 and 2, and their total. Note that N1 = K1 × M1.
- R The target value of the allocation ratio of the number of subjects in group 1 and number of subjects in group 2. R = (K1 × M1) / N2. The actual ratio value may not be exactly R because N1 and N2 are integers.
- $\delta$  The mean difference in the response at which the power is calculated.  $\delta = \mu_1 - \mu_2$ .
- $\Theta$  The ratio of the group 1 and group 2 variances. In this case,  $\Theta = (\sigma_u^2 + \sigma_e^2) / \sigma_2^2$ . Hence,  $\Theta = 1$  implies that  $\sigma_1^2 = \sigma_2^2 = (\sigma_u^2 + \sigma_e^2)$ .
- $\rho$  The intraclass correlation (ICC). The correlation between a (randomly selected) pair of responses within a cluster. In this case,  $\rho = \sigma_u^2 / (\sigma_u^2 + \sigma_e^2)$ .
- $\sigma_u$  The between-cluster standard deviation of the responses in group 1. Note that the variance of subjects in group 1 is  $\sigma_1^2 = \sigma_u^2 + \sigma_e^2$ .
- $\sigma_e$  The within-cluster standard deviation of the responses in group 1. Note that the variance of subjects in group 1 is  $\sigma_1^2 = \sigma_u^2 + \sigma_e^2$ .
- $\sigma_2$  The standard deviation of the subject responses in the non-cluster arm, group 2.
- Alpha The probability of rejecting a true null hypothesis.

### Summary Statements

A parallel, two-group design with cluster-randomized subjects in Group 1 only (and no clustering in Group 2) will be used to test whether the Group 1 mean ( $\mu_1$ ) is different from the Group 2 mean ( $\mu_2$ ) (H0:  $\delta = 0$  versus Ha:  $\delta \neq 0$ ,  $\delta = \mu_1 - \mu_2$ ). The comparison will be made using a two-sided mixed model test, with a Type I error rate ( $\alpha$ ) of 0.05. For Group 2, the subject-to-subject standard deviation is assumed to be 1. For Group 1, the within-cluster standard deviation is assumed to be 0.73485 (calculated from the assumed Group 1 to Group 2 variance ratio 0.9), the between-cluster standard deviation is assumed to be 0.6, the intraclass correlation coefficient is assumed to be 0.4, and the coefficient of variation of cluster sizes is assumed to be 0.65. To detect a mean difference ( $\mu_1 - \mu_2$ ) of 0.5, with 10 subjects per cluster in Group 1 and 200 subjects in Group 2, with 90% power, the number of needed clusters in Group 1 is 30 (totaling 300 subjects in Group 1).

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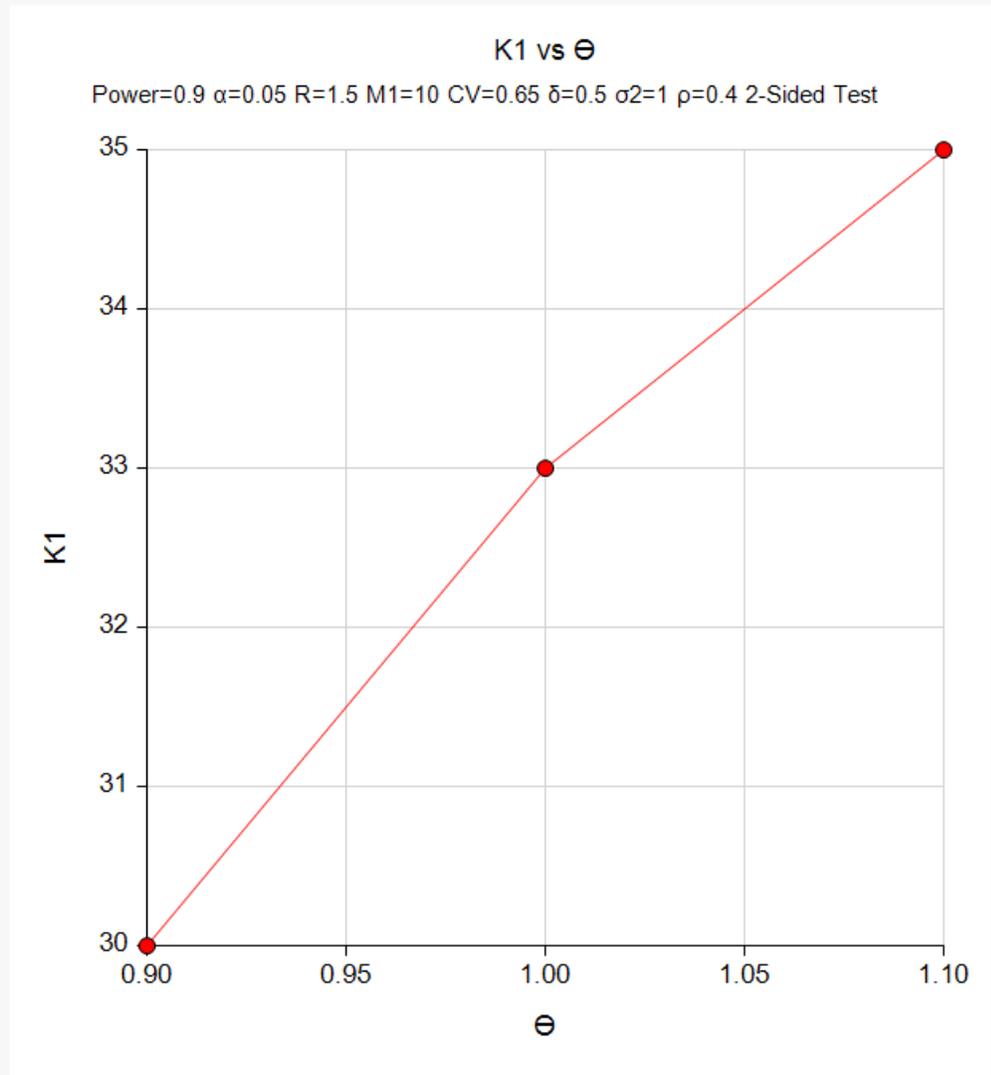
**References**

Moerbeek, M. and Wong, W.K. 2008. 'Sample size formulae for trials comparing group and individual treatments in a multilevel model.' *Statistics in Medicine*, Vol. 27, pages 2850-2864.  
 Julious, Steven A. 2023. *Sample Sizes for Clinical Trials*. Second Edition. CRC Press. New York.  
 Donner, A. and Klar, N. 2000. *Design and Analysis of Cluster Randomization Trials in Health Research*. Arnold. London.

This report shows the power for each of the scenarios.

**Plots Section**

**Plots**



This plot shows the number of clusters versus the variance ratios.

## Example 2 – Validation using Moerbeek and Wong (2008)

Moerbeek and Wong (2008) page 2855 provide a table in which several sample sizes are calculated for a two-sided test. When alpha is 0.05,  $\delta$  is 0.5, COV = 0,  $\theta$  is 0.9,  $\rho$  is 0.1,  $\sigma_2$  is 1.0, N2 is 67, M1 is 5, and K1 is 15, they calculate a power of 0.80.

### 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided (Ha: <math>\delta \neq 0</math>, <math>\delta = \mu_1 - \mu_2</math>)</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter K1 and N2 individually</b>
K1 (Number of Clusters) .....	<b>15</b>
M1 (Average Cluster Size).....	<b>5</b>
COV (Coefficient of Variation of Cluster Sizes).....	<b>0</b>
N2 (Number of Subjects) .....	<b>67</b>
$\delta$ (Mean Difference = $\mu_1 - \mu_2$ ).....	<b>0.5</b>
$\sigma_2$ (Standard Deviation in Group 2) .....	<b>1</b>
$\Theta$ (Group Variance Ratio = $\sigma_1^2 / \sigma_2^2$ ) .....	<b>0.9</b>
$\rho$ (Intracluster Correlation, ICC).....	<b>0.1</b>

### Output

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

Numeric Results													
Solve For:		Power											
Clustering:		Group 1 has Clustering, Group 2 has No Clustering											
Group Allocation:		Enter K1 and N2 individually											
Hypotheses:		H0: $\delta = 0$ vs. Ha: $\delta \neq 0$											
Group 1 Clusters													
Power	Number of Clusters K1	Average Cluster Size M1	Coefficient of Variation of Cluster Sizes COV	Sample Size			Mean Difference $\delta$	Group Variance Ratio $\theta$	ICC $\rho$	Standard Deviation			Alpha
				N1	N2	N				Between $\sigma_u$	Within $\sigma_e$	Group 2 $\sigma_2$	
0.8015	15	5	0	75	67	142	0.5	0.9	0.1	0.3	0.9	1	0.05

PASS calculates the same power value as Moerbeek and Wong (2008). Thus the procedure is validated.

## Example 3 – Validation using Julious (2023)

Julious (2023) page 88 provides a table in which several sample sizes are calculated for a two-sided test. When alpha is 0.05,  $\delta$  is 0.3, COV = 0,  $\theta$  is 1,  $\rho$  is 0.03,  $\sigma_2$  is 1.0, N2 is 234, M1 is 20.555, and K1 is 18, they calculate a power of 0.90.

### 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 3** 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided (Ha: <math>\delta \neq 0</math>, <math>\delta = \mu_1 - \mu_2</math>)</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter K1 and N2 individually</b>
K1 (Number of Clusters) .....	<b>18</b>
M1 (Average Cluster Size).....	<b>20.555</b>
COV (Coefficient of Variation of Cluster Sizes).....	<b>0</b>
N2 (Number of Subjects) .....	<b>234</b>
$\delta$ (Mean Difference = $\mu_1 - \mu_2$ ).....	<b>0.3</b>
$\sigma_2$ (Standard Deviation in Group 2) .....	<b>1</b>
$\theta$ (Group Variance Ratio = $\sigma_1^2 / \sigma_2^2$ ) .....	<b>1</b>
$\rho$ (Intracluster Correlation, ICC) .....	<b>0.03</b>

### Output

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

Numeric Results														
Solve For:	Power													
Clustering:	Group 1 has Clustering, Group 2 has No Clustering													
Group Allocation:	Enter K1 and N2 individually													
Hypotheses:	H0: $\delta = 0$ vs. Ha: $\delta \neq 0$													
<b>Group 1 Clusters</b>														
	Average Cluster Size		Coefficient of Variation of Cluster Sizes	Sample Size			Mean Difference	Group Variance Ratio	Standard Deviation					
<b>Power</b>	<b>Number of Clusters</b>	<b>M1</b>	<b>COV</b>	<b>N1</b>	<b>N2</b>	<b>N</b>	<b><math>\delta</math></b>	<b><math>\theta</math></b>	<b>ICC</b>	<b><math>\rho</math></b>	<b>Between <math>\sigma_u</math></b>	<b>Within <math>\sigma_e</math></b>	<b>Group 2 <math>\sigma_2</math></b>	<b>Alpha</b>
0.90003	18	20.555	0	370	234	604	0.3	1	0.03	0.17321	0.98489	1	0.05	

PASS also calculates a power of 0.90. The procedure is validated.