

## Chapter 484

# Superiority by a Margin Tests for Two Means in a Cluster-Randomized Design

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### Introduction

This procedure computes power and sample size for *superiority by a margin* tests in cluster-randomized designs in which the outcome is a continuous normal random variable.

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 two groups, made up of  $K_i$  clusters of  $M_{ij}$  individuals each, are to be tested using a modified  $z$  test, or  $t$ -test, in which the clusters are treated as subjects. Generally speaking, the larger the cluster sizes and the higher the correlation among subjects within the same cluster, the larger will be the overall sample size necessary to detect an effect with the same power.

It should be noted that we could not find any published results about superiority testing with cluster-randomized designs. What we could find were Schuirmann's TOST procedure and a discussion of how to adjust the  $t$ -test sample size results given by Campbell and Walters (2014). So, we applied the Campbell and Walters adjustment to Schuirmann's test. We look forward to results that substantiate our approach.

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### The Statistical Hypotheses

Superiority tests are examples of directional (one-sided) tests. This program module provides the input and output in formats that are convenient for these types of tests. This section will review the specifics of superiority testing.

Remember that in the usual  $t$ -test setting, the null ( $H_0$ ) and alternative ( $H_a$ ) hypotheses for one-sided tests are defined as follows, assuming that  $\delta = \mu_1 - \mu_2$  is to be tested.

$$H_0: \delta \leq 0 \text{ versus } H_a: \delta > 0$$

Rejecting this test implies that the mean difference is larger than the value  $\delta$ . This test is called an *upper-tailed test* because it is rejected in samples in which the difference between the sample means is larger than  $D$ .

Following is an example of a *lower-tailed test*.

$$H_0: \delta \geq 0 \text{ versus } H_a: \delta < 0$$

*Superiority* tests are special cases of the above directional tests. It will be convenient to adopt the following specialized notation for the discussion of these tests.

## Superiority by a Margin Tests for Two Means in a Cluster-Randomized Design

<u>Parameter</u>	<u>PASS Input/Output</u>	<u>Interpretation</u>
$\mu_1$	Not used	<i>Mean</i> of population 1. Population 1 is assumed to consist of those who have received the new treatment.
$\mu_2$	Not used	<i>Mean</i> of population 2. Population 2 is assumed to consist of those who have received the reference treatment.
$\varepsilon$	SM	<i>Margin of superiority</i> . This is a tolerance value that defines the magnitude of the amount that is not of practical importance. This may be thought of as the smallest change from the baseline that is considered to be different.
$\delta$	$\delta$	<i>True difference</i> . This is the value of $\mu_1 - \mu_2$ , the difference between the means.

Note that the actual values of  $\mu_1$  and  $\mu_2$  are not needed. Only their difference is needed for power and sample size calculations.

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### Superiority Tests

A *non-inferiority test* tests that the treatment mean is not worse than the reference mean by more than the non-inferiority margin. The actual direction of the hypothesis depends on the response variable being studied.

#### Case 1: High Values Good, Superiority Test

In this case, higher values are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment mean is no less than a small amount below the reference mean. The value of  $\delta$  must be greater than  $\varepsilon$ . The following are equivalent sets of hypotheses.

$$H_0: \delta \leq \varepsilon \text{ versus } H_a: \delta > \varepsilon, \quad \varepsilon > 0$$

$$H_0: \mu_1 - \mu_2 \leq \varepsilon \text{ versus } H_a: \mu_1 - \mu_2 > \varepsilon, \quad \varepsilon > 0$$

$$H_0: \mu_1 \leq \mu_2 + \varepsilon \text{ versus } H_a: \mu_1 > \mu_2 + \varepsilon, \quad \varepsilon > 0$$

#### Case 2: High Values Bad, Superiority Test

In this case, lower values are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment mean is less than the reference mean by at least the margin of superiority. The value of  $\delta$  must be less than  $-|\varepsilon|$ . The following are equivalent sets of hypotheses.

$$H_0: \delta \geq -\varepsilon \text{ versus } H_a: \delta < -\varepsilon, \quad \varepsilon > 0$$

$$H_0: \mu_1 - \mu_2 \geq -\varepsilon \text{ versus } H_a: \mu_1 - \mu_2 < -\varepsilon, \quad \varepsilon > 0$$

$$H_0: \mu_1 \geq \mu_2 - \varepsilon \text{ versus } H_a: \mu_1 < \mu_2 - \varepsilon, \quad \varepsilon > 0$$

## Technical Details

Our formulation is a combination of superiority formulas given by Chow et al. (2003) pages 57-59 and the cluster-randomized design formulas given in Campbell and Walters (2014) and Ahn, Heo, and Zhang (2015). Denote an observation by  $Y_{ijk}$  where  $i = 1, 2$  gives the group,  $j = 1, 2, \dots, K_i$  gives the cluster within group  $i$ , and  $k = 1, 2, \dots, m_{ij}$  denotes an individual in cluster  $j$  of group  $i$ .

We let  $\sigma^2$  denote the variance of  $Y_{ijk}$ , which is  $\sigma_{Between}^2 + \sigma_{Within}^2$ , where  $\sigma_{Between}^2$  is the variation between clusters and  $\sigma_{Within}^2$  is the variation within clusters. Also, let  $\rho$  denote the intraclass correlation coefficient (ICC) which is  $\sigma_{Between}^2 / (\sigma_{Between}^2 + \sigma_{Within}^2)$ . This correlation is the simply correlation between any two observations in the same cluster.

For sample size calculation, we assume that the  $m_{ij}$  are distributed with a mean cluster size of  $M_i$  and a coefficient of variation cluster sizes of  $COV$ . The variance of the two group means,  $\bar{Y}_i$ , are approximated by

$$V_i = \frac{\sigma^2 (DE_i)(RE_i)}{K_i M_i}$$

$$DE_i = 1 + (M_i - 1)\rho$$

$$RE_i = \frac{1}{1 - (COV)^2 \lambda_i (1 - \lambda_i)}$$

$$\lambda_i = M_i \rho / (M_i \rho + 1 - \rho)$$

DE is called the *Design Effect* and RE is the *Relative Efficiency* of unequal to equal cluster sizes. Both are greater than or equal to one, so both inflate the variance.

Assume that  $\delta = \mu_1 - \mu_2$  is to be tested using a modified two-sample t-test. Assuming that higher values are better, the non-inferiority test statistic is

$$t = \frac{\bar{Y}_1 - \bar{Y}_2 - \varepsilon}{\sqrt{\hat{V}_1 + \hat{V}_2}}$$

We assume this statistic has an approximate t distribution with degrees of freedom  $DF = K_1 M_1 + K_2 M_2 - 2$  for a *subject-level* analysis or  $K_1 + K_2 - 2$  for a *cluster-level* analysis.

Define the noncentrality parameter as  $\Delta = (\delta - \varepsilon) / \sigma_d$ , where  $\sigma_d = \sqrt{V_1 + V_2}$ . We can define the critical value based on a central t-distribution with DF degrees of freedom as follows.

$$X = t_{\alpha, DF}$$

The power can be found from the following to probabilities

$$\text{Power} = 1 - H_{X, DF, \Delta}$$

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

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## 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.

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### Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

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#### Solve For

##### Solve For

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

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

Note that the value selected here always appears as the vertical axis on the charts.

The program is set up to calculate power directly. To find appropriate values of the other parameters, a binary search is made using an iterative procedure until an appropriate value is found.

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#### Test

##### Higher Means Are

This option defines whether higher values of the response variable are to be considered better or worse. The choice here determines the direction of the non-inferiority test.

If Higher Means Are *Better* the null hypothesis is  $\delta \leq SM$  and the alternative hypothesis is  $\delta > SM$ . If Higher Means Are *Worse* the null hypothesis is  $\delta \geq -SM$  and the alternative hypothesis is  $\delta < -SM$ .

##### Test Statistic

Specify which t-test statistic you are going to use: a t-test based on the number of subjects or a t-test in which the cluster means are treated as subjects.

- **T-Test Based on Number of Subjects**

This uses the methodology shown in the recent books by Campbell and Walters (2014) and Ahn, Heo, and Zhang (2015). In this case, power is based on a t-test in which the variance is inflated to adjust for the clustering and the degrees of freedom is based on to the number of subjects.

- **T-Test Based on Number of Clusters**

This uses the original methodology of Donner and Klar (1996). In this case, power is based on a t-test in which the variance is also inflated to adjust for the clustering, but the degrees of freedom are based on the number of clusters. Donner and Klar ignored the impact of COV, so, if you want to match their results, you should set the COV to zero.

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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.

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 or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

If your only interest is in determining the appropriate sample size for a confidence interval, set power to 0.5.

### 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 0.025 is used for alpha of one-sided test and this has become a standard.

You may enter a range of values such as *0.025 0.05 0.10* or *0.01 to 0.10 by 0.01*.

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## Sample Size – Number of Clusters & Cluster Size

### Group 1 (Treatment)

#### K1 (Number of Clusters)

Enter a value (or range of values) for the number of clusters in the treatment group. You may enter a range of values such as *10 to 20 by 2*. The sample size for this group is equal to the number of clusters times the average cluster size.

#### M1 (Average Cluster Size)

This is the average number of subjects per cluster in group one. This value must be a positive number that is at least one. You can use a list of values such as *100 150 200*.

### Group 2 (Control)

#### K2 (Number of Clusters)

This is the number of clusters in group two. This value must be a positive number. The sample size for this group is equal to the number of clusters times the number of subjects per cluster.

If you simply want a multiple of the value for group one, you would enter the multiple followed by *K1*, with no blanks. If you want to use *K1* directly, you do not have to premultiply by *1*. For example, all of the following are valid entries: *10 K1 2K1 0.5K1 K1*.

You can use a list of values such as *10 20 30* or *K1 2K1 3K1*.

#### M2 (Average Cluster Size)

This is the average number of subjects per cluster in group two. This value must be at least one.

If you simply want a multiple of the value for group one, you would enter the multiple followed by *M1*, with no blanks. If you want to use *M1* directly, you do not have to premultiply by *1*. For example, all of the following are valid entries: *10M1 2M1 0.5M1 M1*.

You can use a list of values such as *10 20 30* or *M1 2M1 3M1*.

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**Coefficient of Variation of Cluster Sizes****COV of Cluster Sizes**

Enter the *coefficient of variation* of the cluster sizes (number of subjects). This value must be zero or a positive number. The COV of X is defined as the standard deviation of X divided by the mean of X.

Campbell and Walters (2014) page 71 give guidance on the possible values of COV. They indicate that as the average cluster size increases, COV tends toward 0.65. They say that typical values of COV range from 0.4 to 0.9.

You can use a list of values such as *0.4 0.6 0.8*.

**Standard Deviation**

The standard deviation, calculated by the sample formula (divide by n-1), is a measure of the variability. When no other information is available, Campbell and Walters (2014) page 71 suggest using (Maximum Cluster Size - Minimum Cluster Size) / 4.

**All Cluster Sizes Equal**

When all cluster sizes are equal, the coefficient of variation is zero.

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**Effect Size****SM (Superiority Margin)**

This is the magnitude of the margin of superiority. It must be a positive number.

When higher means are better, this value is the shortest distance above the reference mean at which the treatment mean is considered superior.

When higher means are worse, this value is the shortest distance below the reference mean at which the treatment mean is considered superior.

 **$\delta$  (Mean Difference =  $\mu_1 - \mu_2$ )**

This is the actual difference between the treatment group mean and the reference group mean.

When higher means are better,  $\delta > SM$ . When higher means are worse,  $\delta < -SM$ .

 **$\sigma$  (Standard Deviation)**

Enter the subject-to-subject standard deviation. This standard deviation applies for both groups.

Note that  $\sigma$  must be a positive number. You can enter a single value such as *5* or a series of values such as *1 3 5 7 9* or *1 to 9 by 2*.

Press the small 'σ' button to the right to obtain calculation options for estimating the standard deviation.

 **$\rho$  (Intracluster Correlation, ICC)**

This is the value of the intracluster correlation coefficient. It may be interpreted as the correlation between any two observations in the same cluster. It may also be thought of as the proportion of the variation in response that can be accounted for by the between-cluster variation.

Possible values are from 0 to just below 1. Typical values are between 0.0001 and 0.05.

You may enter a single value or a list of values.

## Example 1 – Calculating Power

Suppose a superiority test is to be conducted on data obtained from a cluster-randomized design in which  $SM= 1$ ;  $\delta = 2$ ;  $\sigma = 4$ ;  $\rho = 0.0, 0.05, \text{ and } 0.10$ ;  $M1 \text{ and } M2 = 10$ ;  $COV = 0.65$ ;  $alpha = 0.025$ ; and  $K1 \text{ and } K2 = 20, 40, \text{ or } 60$ . Power is to be calculated assuming higher means are better.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Superiority by a Margin Tests for Two Means in a Cluster-Randomized Design** procedure window by expanding **Means**, then **Two Independent Means**, then clicking on **Cluster-Randomized**, and then clicking on **Superiority by a Margin Tests for Two Means in a Cluster-Randomized Design**. 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>Power</b>
Higher Means Are.....	<b>Better (Ha: <math>\delta &gt; SM</math>)</b>
Test Statistic .....	<b>T-Test Based on Number of Subjects</b>
Alpha.....	<b>0.025</b>
K1 (Number of Clusters).....	<b>20 40 60</b>
M1 (Average Cluster Size) .....	<b>10</b>
K2 (Number of Clusters).....	<b>K1</b>
M2 (Average Cluster Size) .....	<b>M1</b>
COV of Cluster Sizes.....	<b>0.65</b>
SM (Superiority Margin).....	<b>1</b>
$\delta$ (Mean Difference = $\mu_1 - \mu_2$ ) .....	<b>2</b>
$\sigma$ (Standard Deviation) .....	<b>4</b>
$\rho$ (Intraclass Correlation, ICC).....	<b>0 0.05 0.1</b>

### Annotated Output

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

### Numeric Results

<b>Numeric Results for a Test of Mean Difference</b>												
Test Statistic: T-Test with DF based on number of subjects												
Higher Means are Better												
Hypotheses: $H_0: \delta \leq SM$ vs. $H_1: \delta > SM$												
	Subj Cnt	Subj Cnt	Clus Cnt	Clus Cnt	Clus Size	Clus Size	COV Clus Size	Diff $\mu_1 - \mu_2$	Super- iority Margin	Std Dev	ICC $\rho$	Alpha
<b>Power</b>	<b>N1</b>	<b>N2</b>	<b>K1</b>	<b>K2</b>	<b>M1</b>	<b>M2</b>	<b>COV</b>	<b><math>\delta</math></b>	<b>SM</b>	<b><math>\sigma</math></b>	<b><math>\rho</math></b>	<b>Alpha</b>
0.7033	200	200	20	20	10	10	0.650	2.00	1.00	4.00	0.000	0.025
0.9423	400	400	40	40	10	10	0.650	2.00	1.00	4.00	0.000	0.025
0.9911	600	600	60	60	10	10	0.650	2.00	1.00	4.00	0.000	0.025
0.5039	200	200	20	20	10	10	0.650	2.00	1.00	4.00	0.050	0.025
0.7973	400	400	40	40	10	10	0.650	2.00	1.00	4.00	0.050	0.025
0.9278	600	600	60	60	10	10	0.650	2.00	1.00	4.00	0.050	0.025
0.4018	200	200	20	20	10	10	0.650	2.00	1.00	4.00	0.100	0.025
0.6795	400	400	40	40	10	10	0.650	2.00	1.00	4.00	0.100	0.025
0.8440	600	600	60	60	10	10	0.650	2.00	1.00	4.00	0.100	0.025

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### References

- 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.
- Julious, Steven A. 2010. Sample Sizes for Clinical Trials. CRC Press. New York.
- Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.
- Donner, A. and Klar, N. 1996. 'Statistical Considerations in the Design and Analysis of Community Intervention Trials'. J. Clin. Epidemiol. Vol 49, No. 4, pages 435-439.
- Donner, A. and Klar, N. 2000. Design and Analysis of Cluster Randomization Trials in Health Research. Arnold. London.
- Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

### Report Definitions

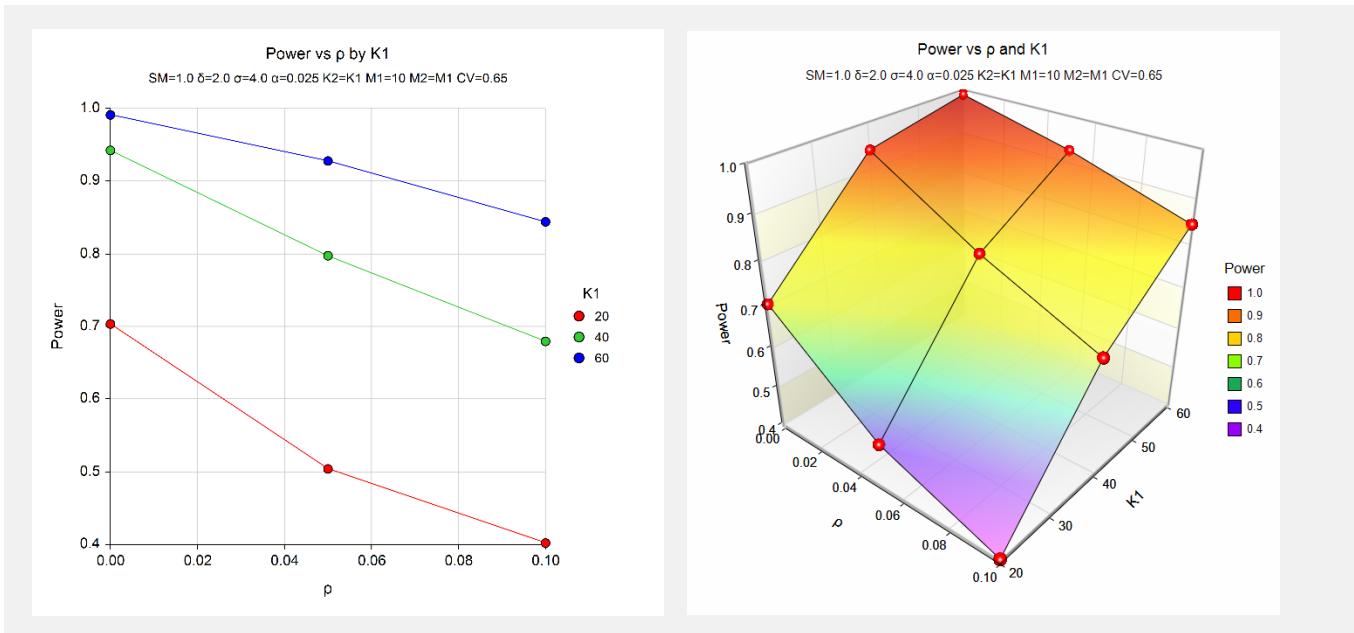
- Power is the probability of rejecting a false null hypothesis. It should be close to one.
- N1 and N2 are the number of subjects in groups 1 and 2, respectively.
- K1 and K2 are the number of clusters in groups 1 and 2, respectively.
- M1 and M2 are the average number of items (subjects) per cluster in groups 1 and 2, respectively.
- SM is the superiority margin. Since higher means are better, this value is positive and is the distance above the group two (reference) mean that is still considered superior.
- COV is the coefficient of variation of the cluster sizes.
- $\delta$  is the mean difference ( $\mu_1 - \mu_2$ ) in the response at which the power is calculated.
- $\sigma$  is the standard deviation of the subject responses.
- $\rho$  (ICC) is the intraclass correlation.
- Alpha is the probability of rejecting a true null hypothesis, that is, rejecting when the means are actually equal.

### Summary Statements

Sample sizes of 200 in group one and 200 in group two, which were obtained by sampling 20 clusters with an average of 10 subjects each in group one and 20 clusters with an average of 10 subjects each in group two, achieve 70% power to detect superiority. The margin of superiority is 1.00. The true difference between the means is assumed to be 2.00. The standard deviation of subjects is 4.00. The intraclass correlation coefficient is 0.000. The coefficient of variation of cluster sizes is 0.650. A one-sided, two-sample t-test was used with a significance level of 0.025. This test used degrees of freedom based on the number of subjects.

This report shows the power for each of the scenarios.

### Plots Section



These plots show the results of the various scenarios specified.



## Example 2 – Validation using Another PASS Procedure

We could not find a validation example for this procedure, so we will compare the results with those of the *Two-Sample T-Tests for Superiority by a Margin Assuming Equal Variance* procedure. The results should be identical when  $M1 = M2 = 1$ . Use the following scenario: find  $K1$  when  $\delta = 2$ ,  $SM = 1$ ,  $\sigma = 3$ ,  $\alpha = 0.025$ , and  $\text{power} = 0.90$ . That procedure obtained a value of 191 for  $K1$  and  $K2$ .

Because  $M1 = 1$ , the values of  $\rho$  and  $COV$  are set to 0.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Superiority by a Margin Tests for Two Means in a Cluster-Randomized Design** procedure window by expanding **Means**, then **Two Independent Means**, then clicking on **Cluster-Randomized**, and then clicking on **Superiority by a Margin Tests for Two Means in a Cluster-Randomized Design**. 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>K1 (Number of Clusters)</b>
Higher Means Are.....	<b>Better (Ha: <math>\delta &gt; SM</math>)</b>
Test Statistic .....	<b>T-Test Based on Number of Subjects</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.025</b>
M1 (Average Cluster Size) .....	<b>1</b>
K2 (Number of Clusters).....	<b>K1</b>
M2 (Average Cluster Size) .....	<b>M1</b>
COV of Cluster Sizes.....	<b>0</b>
SM (Superiority Margin).....	<b>1</b>
$\delta$ (Mean Difference = $\mu_1 - \mu_2$ ) .....	<b>2</b>
$\sigma$ (Standard Deviation) .....	<b>3</b>
$\rho$ (Intracluster Correlation, ICC).....	<b>0</b>

### Output

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

### Numeric Results

Numeric Results for a Test of Mean Difference												
Test Statistic: T-Test with DF based on number of subjects												
Higher Means are Better												
Hypotheses: $H_0: \delta \leq SM$ vs. $H_1: \delta > SM$												
	Subj Cnt	Subj Cnt	Clus Cnt	Clus Cnt	Clus Size	Clus Size	COV Clus Sizes	Diff $\mu_1 - \mu_2$	Super- iority Margin	Std Dev	ICC $\rho$	Alpha
Power	N1	N2	K1	K2	M1	M2	COV	$\delta$	SM	$\sigma$	$\rho$	Alpha
0.9013	191	191	191	191	1	1	0.000	2.00	1.00	3.00	0.000	0.025

PASS also calculates  $K1$  to be 191.