

## Chapter 237

# Superiority by a Margin Tests for the Difference of Two Proportions in a Cluster-Randomized Design

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### Introduction

This module provides power analysis and sample size calculation for superiority by a margin tests of the difference in two-sample, cluster-randomized designs in which the outcome is binary.

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### Technical Details

Our formulation comes from Donner and Klar (2000). Denote a binary observation by  $Y_{gkm}$  where  $g = 1$  or  $2$  is the group,  $k = 1, 2, \dots, K_g$  is a cluster within group  $g$ , and  $m = 1, 2, \dots, M_g$  is an individual in cluster  $k$  of group  $g$ . The results that follow assume an equal number of individuals per cluster. When the number of subjects from cluster to cluster are about the same, the power and sample size values should be fairly accurate. In these cases, the average number of subjects per cluster can be used.

The statistical hypothesis that is tested concerns the difference between the two group proportions,  $p_1$  and  $p_2$ . When necessary, we assume that group 1 is the treatment group and group 2 is the control group. With a simple modification, all of the large-sample sample size formulas that are listed in the module for testing two proportions can be used here.

When the individual subjects are randomly assigned to one of the two groups, the variance of the sample proportion is

$$\sigma_{S,g}^2 = \frac{p_g(1-p_g)}{n_g}$$

## Superiority by a Margin Tests for the Difference of Two Proportions in a Cluster-Randomized Design

When the randomization is by clusters of subjects, the variance of the sample proportion is

$$\begin{aligned}\sigma_{C,g}^2 &= \frac{p_g(1-p_g)(1+(m_g-1)\rho)}{k_g m_g} \\ &= \sigma_{S,g}^2 [1+(m_g-1)\rho] \\ &= F_{g,\rho} \sigma_{S,g}^2\end{aligned}$$

The factor  $[1+(m_g-1)\rho]$  is called the *inflation factor*. The Greek letter  $\rho$  is used to represent the *intracluster correlation coefficient (ICC)*. This correlation may be thought of as the simple correlation between any two subjects within the same cluster. If we stipulate that  $\rho$  is positive, it may also be interpreted as the proportion of total variability that is attributable to differences between clusters. This value is critical to the sample size calculation.

The asymptotic formulas that were used in comparing two proportions (see Chapter 195, “Superiority by a Margin Tests for the Difference Between Two Proportions”) may be used with cluster-randomized designs as well, as long as an adjustment is made for the inflation factor.

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## Power Calculations

A large sample approximation may be used that is most accurate when the values of  $n_1$  and  $n_2$  are large. The large approximation is made by replacing the values of  $\hat{p}_1$  and  $\hat{p}_2$  in the  $z$  statistic with the corresponding values of  $p_1$  and  $p_2$  under the alternative hypothesis, and then computing the results based on the normal distribution.

Note that in this case, exact calculations are not possible.

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## Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design and Options tabs. 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 the parameters associated with this test such as the proportions, sample sizes, alpha, and power.

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### Solve For

#### Solve For

This option specifies the parameter to be solved for using the other parameters. The parameters that may be selected are *Power*, *Sample Size (K1)*, *Sample Size (M1)*, *Effect Size*, and *ICC*. Under most situations, you will select either *Power* or *Sample Size (K1)*.

Select *Sample Size (K1)* when you want to calculate the number of clusters per group needed to achieve a given power and alpha level.

Select *Power* when you want to calculate the power of an experiment.

## Test

### Higher Proportions Are

Use this option to specify the direction of the test.

If Higher Proportions are “Better”, the alternative hypothesis is  $H1: P1 - P2 > D0$ .

If Higher Proportions are “Worse”, the alternative hypothesis is  $H1: P1 - P2 < D0$ .

### Test Type

Specify which test statistic is used in searching and reporting. We recommend the likelihood score test.

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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 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.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

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 – Group 1 (Treatment)

### K1 (Clusters in Group 1)

Enter a value (or range of values) for the number of clusters in group one. 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 number of subjects per cluster.

### M1 (Items per Cluster in Group 1)

This is the average number of items (subjects) per cluster in group one. This value must be a positive number that is at least 1. You can use a list of values such as *100 150 200*.

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## Sample Size – Group 2 (Reference)

### K2 (Clusters in Group 2)

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

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 pre-multiply by 1. For example, all of the following are valid entries: *10 K1 2K1 0.5K1*.

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

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### M2 (Items per Cluster in Group 2)

This is the number of items (subjects) per cluster in group two. This value must be a positive number.

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 pre-multiply by *I*. For example, all of the following are valid entries: *10 M1 2M1 0.5M1*.

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

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## Effect Size

### Input Type

Indicate what type of values to enter to specify the differences. 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 differences.

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### Effect Size – Differences (P1 – P2)

*These options are displayed only if Input Type = “Differences”*

#### D0 (Superiority Difference)

This option specifies the trivial difference (often called the *margin of error*) between P1.0 (the value of P1 under H0) and P2. This difference is used with P2 to calculate the value of P1.0 using the formula:  $P1.0 = P2 + D0$ .

When *Higher Proportions Are* is set to *Better*, the trivial difference is that amount by which P1 must be greater than P2 to have the treatment group declared superior to the reference group. D0 should be positive for superiority by a margin tests.

The reverse is the case when *Higher Proportions Are* is set to *worse*.

You may enter a range of values such as *.03 .05 .10* or *.05 to .1 by .01*. Differences must be between -1 and 1. D0 cannot take on the values -1, 0, or 1.

#### D1 (Actual Difference)

This option specifies the actual difference between P1 and P2. This is the value of the difference at which the power is calculated.

The power calculations assume that P1.1 is the actual value of the proportion in group 1 (experimental or treatment group). This difference is used with P2 to calculate the value of P1 using the formula:  $P1.1 = D1 + P2$ .

You may enter a range of values such as *-.05 0 .5* or *-.05 to .05 by .02*. Actual differences must be between -1 and 1. They cannot take on the values -1 or 1.

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### Effect Size – Group 1 (Treatment)

*These options are displayed only if Input Type = “Proportions”*

#### P1.0 (Superiority Proportion)

This option allows you to specify the value P1.0 directly. This is that value of treatment group’s proportion above which the treatment group is considered superior to the reference group.

When *Higher Proportions Are* is set to *Better*, the trivial proportion is the smallest value of P1 for which the treatment group is declared superior to the reference group. P1.0 should be greater than P2 for superiority by a margin tests. The reverse is the case when *Higher Proportions Are* is set to *Worse*.

Proportions must be between 0 and 1. They cannot take on the values 0 or 1. This value should not be set to exactly the value of P2. You may enter a range of values such as *0.03 0.05 0.10* or *0.01 to 0.05 by 0.01*.

**Superiority by a Margin Tests for the Difference of Two Proportions in a Cluster-Randomized Design****P1.1 (Actual Proportion)**

This option specifies the value of P1.1 which is the value of the treatment proportion at which the power is to be calculated. Proportions must be between 0 and 1. They cannot take on the values 0 or 1.

You may enter a range of values such as *0.03 0.05 0.10* or *0.01 to 0.05 by 0.01*.

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**Effect Size – Group 2 (Reference)****P2 (Group 2 Proportion)**

Specify the value of  $p_2$ , the reference, baseline, or control group's proportion. The null hypothesis is that the two proportions differ by no more than a specified amount. Since P2 is a proportion, these values must be between 0 and 1.

You may enter a range of values such as *0.1 0.2 0.3* or *0.1 to 0.9 by 0.1*.

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**Effect Size – Intracluster Correlation****ICC (Intracluster Correlation)**

Enter a value (or range of values) for the intracluster correlation. This correlation may be thought of as the simple correlation between any two observations in the same cluster. It may also be thought of as the proportion of total variance in the observations that can be attributed to difference between clusters.

Although the actual range for this value is between 0 to 1, typical values range from 0.002 to 0.05.

## Example 1 – Finding Power

A study is being designed to establish the superiority of a new treatment compared to the current treatment. Historically, the current treatment has enjoyed a 60% cure rate. The new treatment is hoped to perform better than the current treatment. Thus, the new treatment will be adopted if it is more effective than the current treatment by a clinically significant amount. The researchers will recommend adoption of the new treatment if it has a cure rate of at least 70%.

The researchers will recruit patients from various hospitals. All patients at a particular hospital will receive the same treatment. They anticipate an average of 100 patients per hospital. Based on similar studies, they estimate the intraclass correlation to be 0.002.

The researchers plan to use the Farrington and Manning likelihood score test statistic to analyze the data. They want to study the power of the one-sided Farrington and Manning test at group cluster sizes ranging from 2 to 10 when the superiority difference is 0.1 and the actual cure rate of the new treatment ranges from 71% to 80%. The significance level will be 0.05.

### 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 the Difference of Two Proportions in a Cluster-Randomized Design** procedure window by expanding **Proportions**, then **Two Proportions (Cluster-Randomized)**, then clicking on **Superiority by a Margin**, and then clicking on **Superiority by a Margin Tests for the Difference of Two Proportions 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 Proportions Are .....	<b>Better (H1: P1 - P2 &gt; D0)</b>
Test Type .....	<b>Likelihood Score (Farr. &amp; Mann.)</b>
Alpha .....	<b>0.05</b>
K1 (Clusters in Group 1) .....	<b>2 4 6 8 10</b>
M1 (Items per Cluster in Group 1) .....	<b>100</b>
K2 (Clusters in Group 2) .....	<b>K1</b>
M2 (Items per Cluster in Group 2) .....	<b>M1</b>
Input Type .....	<b>Differences</b>
D0 (Superiority Difference) .....	<b>0.1</b>
D1 (Actual Difference) .....	<b>0.11 0.14 0.17 0.2</b>
P2 (Group 2 Proportion) .....	<b>0.6</b>
ICC (Intraclass Correlation) .....	<b>0.002</b>

## Output

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

### Numeric Results

#### Numeric Results

Test Statistic: Likelihood Score Test (Farrington & Manning)

Hypotheses:  $H_0: P_1 - P_2 \leq D_0$  vs.  $H_1: P_1 - P_2 > D_0$

Power	Group 1 Clusters/ Items K1/M1	Group 2 Clusters/ Items K2/M2	Group 2 Prop P2	Group 1 Superior. Prop P1.0	Group 1 Actual Prop P1.1	Superior. Diff D0	Actual Diff D1	Intra- Cluster Corr. ICC	Alpha
0.07313	2/100	2/100	0.6000	0.7000	0.7100	0.1000	0.1100	0.0020	0.050
0.08492	4/100	4/100	0.6000	0.7000	0.7100	0.1000	0.1100	0.0020	0.050
0.09489	6/100	6/100	0.6000	0.7000	0.7100	0.1000	0.1100	0.0020	0.050
0.10394	8/100	8/100	0.6000	0.7000	0.7100	0.1000	0.1100	0.0020	0.050
0.11243	10/100	10/100	0.6000	0.7000	0.7100	0.1000	0.1100	0.0020	0.050
0.19326	2/100	2/100	0.6000	0.7000	0.7400	0.1000	0.1400	0.0020	0.050
0.29446	4/100	4/100	0.6000	0.7000	0.7400	0.1000	0.1400	0.0020	0.050
0.38568	6/100	6/100	0.6000	0.7000	0.7400	0.1000	0.1400	0.0020	0.050
0.46812	8/100	8/100	0.6000	0.7000	0.7400	0.1000	0.1400	0.0020	0.050
0.54203	10/100	10/100	0.6000	0.7000	0.7400	0.1000	0.1400	0.0020	0.050
0.39804	2/100	2/100	0.6000	0.7000	0.7700	0.1000	0.1700	0.0020	0.050
0.62615	4/100	4/100	0.6000	0.7000	0.7700	0.1000	0.1700	0.0020	0.050
0.77839	6/100	6/100	0.6000	0.7000	0.7700	0.1000	0.1700	0.0020	0.050
0.87328	8/100	8/100	0.6000	0.7000	0.7700	0.1000	0.1700	0.0020	0.050
0.92957	10/100	10/100	0.6000	0.7000	0.7700	0.1000	0.1700	0.0020	0.050
0.64643	2/100	2/100	0.6000	0.7000	0.8000	0.1000	0.2000	0.0020	0.050
0.88913	4/100	4/100	0.6000	0.7000	0.8000	0.1000	0.2000	0.0020	0.050
0.96934	6/100	6/100	0.6000	0.7000	0.8000	0.1000	0.2000	0.0020	0.050
0.99221	8/100	8/100	0.6000	0.7000	0.8000	0.1000	0.2000	0.0020	0.050
0.99814	10/100	10/100	0.6000	0.7000	0.8000	0.1000	0.2000	0.0020	0.050

#### Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

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.

P2 is the proportion for group 2, the standard, reference, baseline, or control group.

P1.0 is the proportion for group 1 (the treatment group) assuming the null hypothesis (H0).

P1.1 is the proportion for group 1 (the treatment group) assuming the alternative hypothesis (H1).

D0 = P1.0 - P2 is the superiority difference. It is the difference assuming H0.

D1 = P1.1 - P2 is the actual difference at which the power is calculated.

ICC is the intracluster correlation.

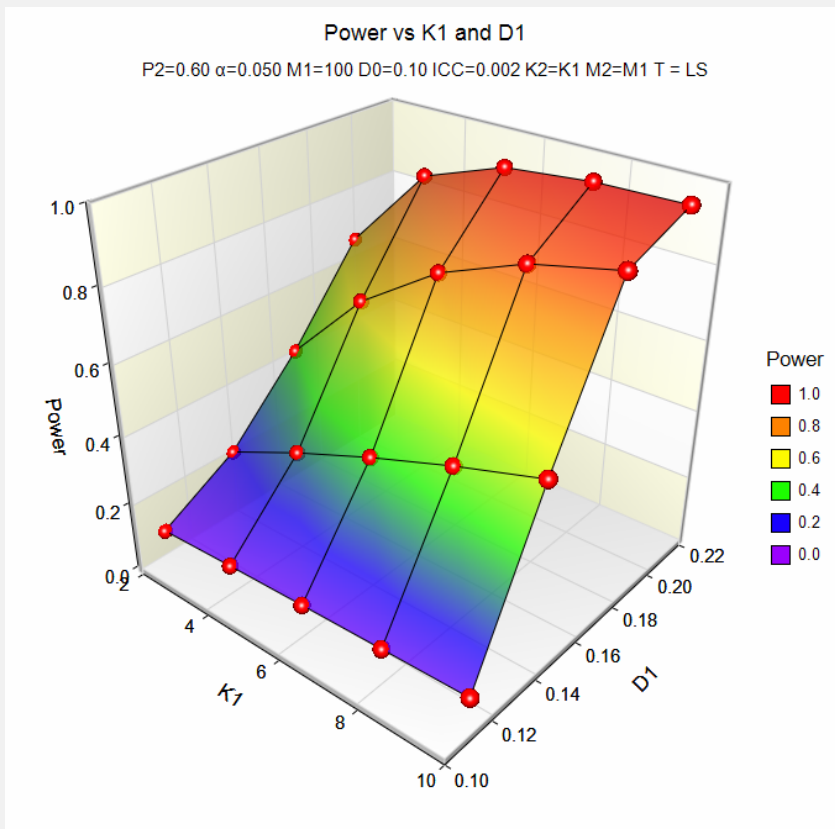
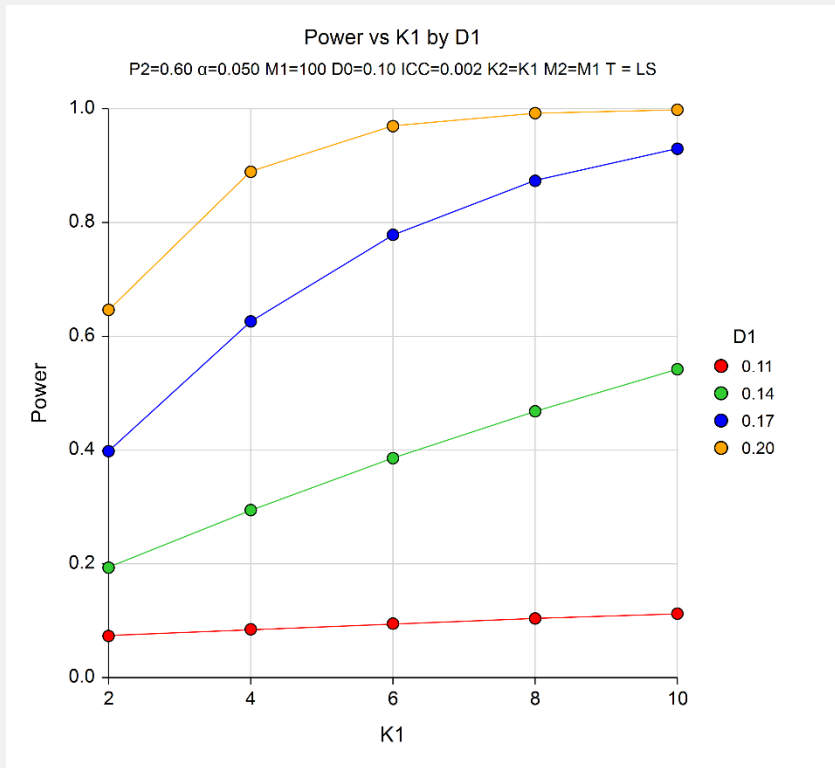
Alpha is the probability of rejecting a true null hypothesis.

#### Summary Statements

Sample sizes of 200 in group 1 and 200 in group 2, which were obtained by sampling 2 clusters with 100 subjects each in group 1 and 2 clusters with 100 subjects each in group 2, achieve 7.313% power to detect a difference of 0.1100 when the superiority difference is 0.1000. The proportion in group 1 (the treatment group) is assumed to be 0.7000 under the null hypothesis and 0.7100 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.6000. The test statistic used is the one-sided Likelihood Score Test (Farrington & Manning). The intracluster correlation is 0.0020, and the significance level of the test is 0.050.

This report shows the values of each of the parameters, one scenario per row. The total number of items sampled in group 1 is  $N_1 = K_1 \times M_1$ . The total number of items sampled in group 2 is  $N_2 = K_2 \times M_2$ .

Plots Section



The values from the table are displayed on the above charts. These charts give a quick look at the sample sizes that will be required for various values of D1.



## Example 2 – Finding the Sample Size (Number of Clusters)

Continuing with the scenario given in Example 1, the researchers want to determine the number of clusters necessary for each value of D1 when the target power is set to 0.80.

### 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 the Difference of Two Proportions in a Cluster-Randomized Design** procedure window by expanding **Proportions**, then **Two Proportions (Cluster-Randomized)**, then clicking on **Superiority by a Margin**, and then clicking on **Superiority by a Margin Tests for the Difference of Two Proportions 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>Sample Size (K1)</b>
Higher Proportions Are .....	<b>Better (H1: P1 - P2 &gt; D0)</b>
Test Type .....	<b>Likelihood Score (Farr. &amp; Mann.)</b>
Power .....	<b>0.80</b>
Alpha .....	<b>0.05</b>
M1 (Items per Cluster in Group 1) .....	<b>100</b>
K2 (Clusters in Group 2) .....	<b>K1</b>
M2 (Items per Cluster in Group 2) .....	<b>M1</b>
Input Type .....	<b>Differences</b>
D0 (Superiority Difference) .....	<b>0.1</b>
D1 (Actual Difference) .....	<b>0.11 0.14 0.17 0.2</b>
P2 (Group 2 Proportion) .....	<b>0.6</b>
ICC (Intracluster Correlation) .....	<b>0.002</b>

### Output

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

### Numeric Results

Numeric Results									
Test Statistic: Likelihood Score Test (Farrington & Manning)									
Hypotheses: H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 > D0									
	Group 1	Group 2		Group 1	Group 1			Intra-	
	Clusters/	Clusters/	Group 2	Superior.	Actual	Superior.	Actual	Cluster	
Power	Items	Items	Prop	Prop	Prop	Diff	Diff	Corr.	Alpha
	K1/M1	K2/M2	P2	P1.0	P1.1	D0	D1	ICC	
0.80034	331/100	331/100	0.6000	0.7000	0.7100	0.1000	0.1100	0.0020	0.050
0.81458	21/100	21/100	0.6000	0.7000	0.7400	0.1000	0.1400	0.0020	0.050
0.83175	7/100	7/100	0.6000	0.7000	0.7700	0.1000	0.1700	0.0020	0.050
0.88913	4/100	4/100	0.6000	0.7000	0.8000	0.1000	0.2000	0.0020	0.050

The required sample size depends a great deal on the value of D1. The researchers should spend time determining the most appropriate value for D1.

## Example 3 – Finding Power after an Experiment

A group of researchers want to show that a new treatment works better than the current treatment. They believe, in fact, that the new treatment is about 0.20 higher in proportion of success. One hundred patients at each of 10 randomly chosen hospitals were given the current treatment. One hundred patients at each of 10 randomly chosen hospitals were given the new treatment. It was agreed before the experiment that the new treatment needed to be greater than 0.1 in proportion of success above the current treatment to be considered superior. The proportion of patients responding to the current treatment was  $721/1000 = 0.721$ . The proportion of patients responding to the new treatment was  $835/1000 = 0.835$ . This result did not show significant superiority at the 0.05 level. The researchers want to know the power of their superiority by a margin test. They decide to use the intraclass correlation coefficient estimated from the data, which was 0.0068. Although the observed difference in proportions is  $0.835 - 0.721 = 0.114$ , the trivial difference is still 0.1. This value is used in the power calculation.

### 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 the Difference of Two Proportions in a Cluster-Randomized Design** procedure window by expanding **Proportions**, then **Two Proportions (Cluster-Randomized)**, then clicking on **Superiority by a Margin**, and then clicking on **Superiority by a Margin Tests for the Difference of Two Proportions in a Cluster-Randomized Design**. You may then make the appropriate entries as listed below, or open **Example 3** 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 Proportions Are .....	<b>Better (H1: P1 - P2 &gt; D0)</b>
Test Type .....	<b>Likelihood Score (Farr. &amp; Mann.)</b>
Alpha .....	<b>0.05</b>
K1 (Clusters in Group 1) .....	<b>10</b>
M1 (Items per Cluster in Group 1) .....	<b>100</b>
K2 (Clusters in Group 2) .....	<b>K1</b>
M2 (Items per Cluster in Group 2) .....	<b>M1</b>
Input Type .....	<b>Differences</b>
D0 (Superiority Difference) .....	<b>0.1</b>
D1 (Actual Difference) .....	<b>0.114 0.2</b>
P2 (Group 2 Proportion) .....	<b>0.721</b>
ICC (Intraclass Correlation) .....	<b>0.0068</b>

## Output

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

### Numeric Results

#### Numeric Results

Test Statistic: Likelihood Score Test (Farrington & Manning)

Hypotheses:  $H_0: P_1 - P_2 \leq D_0$  vs.  $H_1: P_1 - P_2 > D_0$

	Group 1 Clusters/ Items	Group 2 Clusters/ Items	Group 2 Prop P2	Group 1 Superior. Prop P1.0	Group 1 Actual Prop P1.1	Superior. Diff D0	Actual Diff D1	Intra- Cluster Corr. ICC	Alpha
Power	K1/M1	K2/M2							
0.14515	10/100	10/100	0.7210	0.8210	0.8350	0.1000	0.1140	0.0068	0.050
0.99877	10/100	10/100	0.7210	0.8210	0.9210	0.1000	0.2000	0.0068	0.050

If indeed the new treatment were 0.20 higher in proportion of success, the power for showing superiority by a margin would be 0.99877. If the true difference is 0.114, the power would be 0.14515.

## Example 4 – Validation

This procedure uses the same mechanics as the Tests for Two Proportions in a Cluster-Randomized Design procedure. We refer the user to Example 4 of Chapter 230 for the validation.