Chapter 609

# Multi-Arm Superiority by a Margin Tests for the Ratio of Treatment and Control Proportions in a Cluster-Randomized Design

## Introduction

This module computes power and sample size for multi-arm superiority by a margin tests of the ratio of treatment and control proportions when binary data are gathered from a cluster-randomized design. The formulas are based on results in Donner and Klar (2000) and Machin, Campbell, Tan, and Tan (2018).

A *cluster (group) randomized design* is one in which whole units, or clusters, of subjects are randomized to the groups rather than the individual subjects in those clusters. The conclusions of the study concern individual subjects rather than the clusters. Examples of clusters are families, school classes, neighborhoods, hospitals, and doctor's practices.

Cluster-randomized designs are often adopted when there is a high risk of contamination if cluster members were randomized individually. For example, it may be difficult for doctors to use two treatment methods in their practice. The price of randomizing by clusters is a loss of efficiency--the number of subjects needed to obtain a certain level of precision in a cluster-randomized trial is usually much larger than the number needed when the subjects are randomized individually. Hence, standard methods of sample size estimation cannot be used.

In this multi-arm design, there are *G* treatment groups and one control group. A proportion is measured in each group. A total of *G* hypothesis tests are anticipated each comparing a treatment group with the common control group using a z-test of the ratio between two proportions.

The Bonferroni adjustment of the type I error rate may be optionally made because several comparisons are being tested using the same data. Making a multiplicity adjustment is usually recommended, but not always. In fact, Saville (1990) advocates not applying it and Machin, Campbell, Tan, and Tan (2018) include omitting it as a possibility.

## Example

Suppose that the current treatment for a disease works 50% of the time. Unfortunately, this treatment is expensive and occasionally exhibits serious side-effects. Two promising new treatments have been developed and are now ready to be tested. Two superiority by a margin hypotheses need to be tested in this study: whether each new treatment is better than the current treatment by at least a clinically important amount. At least three groups are needed to complete this study of the two new treatments.

Because of the cost of switching to a new treatment, clinicians are willing to adopt a it only if it is substantially more effective than the current treatment. They must determine, however, how much more

effective the new treatment must be to be adopted. Should it be adopted if 52% respond? 55%? 60%? 65%? There is a percentage above 50% at which the ratio between the two treatments is no longer considered ignorable. After thoughtful discussion with several clinicians, it was decided that if a response ratio is at least 0.55, the new treatment will be adopted.

## Multiple Treatments Versus a Single Control

Whether you want to test several doses of a single treatment or several types of treatments, good research practice requires that each treatment be compared with a control. For example, a popular three-arm design consists of three groups: control, treatment A, and treatment B. Two tests are run: treatment A versus control and treatment B versus the same control. This design avoids having to obtain a second control group for treatment B. Besides the obvious efficiency in subjects, it may be easier to recruit subjects if their chances of receiving the new treatment are better than 50-50.

# Technical Details

Our formulation for cluster-randomized designs comes from Donner and Klar (2000). Suppose you have $G$ treatment groups with response probabilities $P_i$ (higher values are better) that have samples of size $N_i$ and one control group with response probability $P_C$ that has a sample of size $N_C$. The total sample size is $N = N_1 + N_2 + \ldots + N_G + N_C$.

The statistical hypotheses to be tested are

$$H_0: P_i \leq P_C(R0) \quad \text{vs.} \quad H_1: P_i > P_C(R0)$$

where $R0$ is the *superiority ratio*. This assumes that $R0 > 1$.

## Cluster-Randomized Designs

Denote a binary (0, 1) observation by $Y_{ikj}$ where $i$ is the group, $k$ = 1, 2, ..., $K_i$ is a cluster within group $i$, and $j$ = 1, 2, ..., $M_i$ is an item (often a subject) in cluster $k$ of group $i$. The results that follow assume an equal number of items per cluster per group. When the number of items 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 items per cluster can be used.

The statistical hypothesis that is tested concerns the ratio between a treatment group proportion and the control group proportion: $P_i$ and $P_C$. With a simple modification, the large-sample sample size formulas that are listed in the module for testing two proportions can be used here.

When the items are randomly assigned to one of the $G + 1$ groups, the variance of the sample proportion is

$$\sigma_{S,i}^2 = \frac{P_i(1 - P_i)}{N_i}$$

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

$$\sigma_{C,i}^2 = \frac{P_i(1-P_i)(1+(M_i-1)\rho)}{K_i M_i}$$

$$= \sigma_{S,i}^2[1+(M_i-1)\rho]$$

$$= F_{i,\rho}\sigma_{S,i}^2$$

The factor $[1+(M_i-1)\rho]$ 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 200, "Tests for Two Proportions") may be used with cluster-randomized designs as well, as long as an adjustment is made for the inflation factor. The basic form of the z-test becomes

$$z = \frac{|\hat{D}|}{\hat{\sigma}_{\hat{D}}(R0)}$$

where

$$\hat{D} = \hat{p}_i - \hat{p}_C R0$$

$$\hat{\sigma}_{\hat{D}}(R0) = \sqrt{\frac{\tilde{p}_i(1-\tilde{p}_i)F_{i,\rho}}{N_i} + \frac{\tilde{p}_C(1-\tilde{p}_C)F_{C,\rho}}{N_C}}$$

The quantities $\tilde{p}_i$ and $\tilde{p}_C$ are the maximum likelihood estimates constrained by $\tilde{p}_i - \tilde{p}_C(R0) = 0$.

## Test Statistic

This procedure assumes that Farrington and Manning (1990) likelihood score test statistic is used for the analysis of the data obtained from this study. This statistic tests whether the response ratio is more than a specified value *R0*. The regular MLE's, $\hat{p}_i$ and $\hat{p}_C$, are used in the numerator of the score statistic while MLE's $\tilde{p}_i$ and $\tilde{p}_C$, constrained so that $\tilde{p}_i/\tilde{p}_C = R0$, are used in the denominator. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{FMD} = \frac{\hat{p}_i - \hat{p}_C(R0)}{\sqrt{\left(\frac{\tilde{p}_i\tilde{q}_i}{N_i/F_{i,\rho}} + \frac{\tilde{p}_C\tilde{q}_C}{N_C/F_{C,\rho}}\right)}}$$

where the estimates $\tilde{p}_i$ and $\tilde{p}_C$ are computed as in the corresponding test of Miettinen and Nurminen (1985) given above.

## Multiplicity Adjustment

Because *G* z-tests between treatment groups and the control group are run when analyzing the results of this study, many statisticians recommend that a Bonferroni adjustment be applied. This adjustment is easy to apply: the value of alpha that is used in the test is found by dividing the original alpha by the number of tests. For example, if the original alpha is set at 0.05 and the number of treatment (not including the control) groups is five, the individual tests should be conducted using an alpha of 0.01.

The main criticism of this procedure is that if there are many tests, the value of alpha becomes very small. To mitigate against this complaint, some statisticians recommend separating the treatment groups into those that are of primary interest and those that are of secondary interest. The Bonferroni adjustment is made by the using the number of primary treatments rather than the total number of treatments.

There are some who advocate ignoring the adjustment entirely in the case of randomized clinical trials. See for example Saville (1990) and the discussion in chapter 14 of Machin, Campbell, Tan, and Tan (2018).

## Size of the Control Group

Because the control group is used over and over, some advocate increasing the number of clusters in this group. The standard adjustment is to include $\sqrt{G}$ clusters in the control group for each cluster in one of the treatment groups. See Machin, Campbell, Tan, and Tan (2018, pages 231-232). Note that often, the treatment groups all have the same sample size.

# Example 1 – Finding the Sample Size

A cluster-randomized, multi-arm trial is being designed to compare two treatments against the standard drug in patients with a specific type of disease. They plan to use the Farrington and Manning likelihood score test based on the response ratio to analyze the data. Historically, the standard treatment has enjoyed a 50% cure rate. The new treatments both reduce the seriousness of certain side effects over the standard treatment and increase the cure rate. Thus, the new treatments will be adopted only if they are more effective than the standard treatment. The researchers will recommend adoption of the either of the new treatments that exhibit a cure rate that is more than 10% greater than the cure rate of the standard treatment. That is, the value of R0 is 1.1. Preliminary estimates of the cure rate of the experiment treatments are at least 65%. Since the control group will be used twice, they set the control group cluster allocation to $\sqrt{G} = \sqrt{2} = 1.414$. The two treatment allocations are set to 1.0.

The researchers will recruit patients from various hospitals. All patients at a particular hospital will receive the same treatment. They anticipate an average of 20 patients per hospital. They want to see the impact on cluster count of having cluster sizes ranging from 10 to 30. The investigators would like a sample size large enough to find statistical significance at the 0.025 level and a power of 0.90 in each test. Based on similar studies, they estimate the intracluster correlation to be 0.002.

## 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 | **Sample Size** |
| Higher Proportions Are | **Better (H1: R > R0)** |
| Power of Each Test | **0.90** |
| Overall Alpha | **0.025** |
| Bonferroni Adjustment | **Standard Bonferroni** |
| Group Allocation | **Enter Group Allocation Pattern, solve for group numbers of clusters** |
| M (Items Per Cluster) | **10 20 30** |
| R0 (Superiority Ratio) | **1.1** |
| Control Proportion | **0.5** |
| Control Items Per Cluster | **M** |
| Control Cluster Allocation | **1.414** |
| Set A Number of Groups | **2** |
| Set A Proportion | **0.65** |
| Set A Items Per Cluster | **M** |
| Set A Cluster Allocation | **1** |
| Set B Number of Groups | **0** |
| Set C Number of Groups | **0** |
| Set D Number of Groups | **0** |
| More | **Unchecked** |
| ρ (Intracluster Correlation) | **0.002** |

# Output

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

## Numeric Reports

**Numeric Results**

| | |
|---|---|
| Solve For: | Sample Size |
| Group Allocation: | Enter Group Allocation Pattern, solve for group numbers of clusters |
| Test Type: | Farrington and Manning Likelihood Score Test |
| Hypotheses: | H0: Ri ≤ R0 vs. H1: Ri > R0 |
| Number of Groups: | 3 |
| Bonferroni Adjustment: | Standard Bonferroni (Divisor = 2) |

| | Power | | Number of Clusters | | Items Per Cluster | Sample Size | | Ratio | | | Alpha | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comparison | Target | Actual | Ki | Cluster Allocation | Mi | Ni | Proportion Pi | Superiority R0 | Actual Ri | ICC ρ | Overall | Bonferroni-Adjusted |
| Control | | | 81 | 1.414 | 10 | 810 | 0.50 | 1.1 | | 0.002 | | |
| vs A1 | 0.9 | 0.90235 | 57 | 1.000 | 10 | 570 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| vs A2 | 0.9 | 0.90235 | 57 | 1.000 | 10 | 570 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| Total | | | 195 | | | 1950 | | | | | | |
| Control | | | 41 | 1.414 | 20 | 820 | 0.50 | 1.1 | | 0.002 | | |
| vs A1 | 0.9 | 0.90098 | 29 | 1.000 | 20 | 580 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| vs A2 | 0.9 | 0.90098 | 29 | 1.000 | 20 | 580 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| Total | | | 99 | | | 1980 | | | | | | |
| Control | | | 28 | 1.414 | 30 | 840 | 0.50 | 1.1 | | 0.002 | | |
| vs A1 | 0.9 | 0.90412 | 20 | 1.000 | 30 | 600 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| vs A2 | 0.9 | 0.90412 | 20 | 1.000 | 30 | 600 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| Total | | | 68 | | | 2040 | | | | | | |

| | |
|---|---|
| Comparison | The group that is involved in the comparison between the treatment and control displayed on this report line. The comparison is made using the ratio. |
| Target Power | The power desired. Power is probability of rejecting a false null hypothesis for this comparison. This power is of the comparison shown on this line only. |
| Actual Power | The power actually achieved. |
| Ki | The number of clusters in the ith group. The total number of clusters is reported in the last row of the column. |
| Allocation | The cluster allocation ratio of the ith group. The value on each row represents the relative number of clusters assigned to the group. |
| Mi | The average number of items per cluster (or average cluster size) in the ith group. |
| Ni | The number of items in the ith group. The total sample size is shown as the last row of the column. |
| Pi | The response proportion in the ith group at which the power is calculated. |
| R0 | The superiority ratio is the ratio boundary between a treatment that is concluded to be superior and a treatment that is not concluded to be superior. |
| Ri | The ratio of the ith group proportion and the control group proportion at which the power is calculated. The formula is Ri = Pi / Pc. |
| ρ | The intracluster correlation (ICC). The correlation between subjects within a cluster. |
| Overall Alpha | The probability of rejecting at least one of the comparisons in this experiment when each null hypothesis is true. |
| Bonferroni Alpha | The adjusted significance level at which each individual comparison is made. |

**Summary Statements**

A parallel, 3-group cluster-randomized design (with one control group and 2 treatment groups) will be used to test whether the proportion for each treatment group is superior to the control group proportion by a margin, with a superiority ratio of 1.1 (H0: R ≤ 1.1 versus H1: R > 1.1, R = Pi / Pc). The hypotheses will be evaluated using 2 one-sided, two-sample, Bonferroni-adjusted (divisor = 2) Farrington and Manning likelihood score tests, with an overall (experiment-wise) Type I error rate (α) of 0.025. The control group proportion is assumed to be 0.5. The intracluster correlation is assumed to be 0.002. The average cluster size (number of subjects or items per cluster) for the control group is assumed to be 10, and the average cluster size for each of the treatment groups is assumed to be 10 and 10. To detect the treatment proportions 0.65 and 0.65 with at least 90% power for each test, the control group cluster count needed will be 81 and the number of needed clusters for the treatment groups will be 57 and 57 (totaling 195 clusters overall).

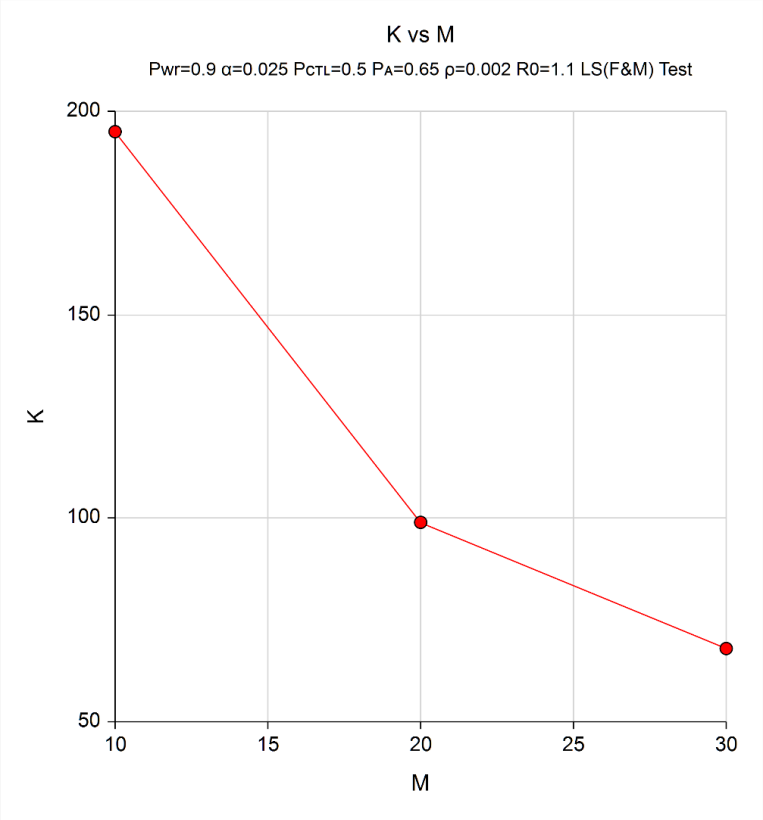
**References**

Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.
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 Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, 3rd Edition. Chapman & Hall/CRC. Boca Raton, FL. Pages 86-88.
Farrington, C. P. and Manning, G. 1990. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statistics in Medicine, Vol. 9, pages 1447-1454.
Gart, John J. and Nam, Jun-mo. 1988. 'Approximate Interval Estimation of the Ratio in Binomial Parameters: A Review and Corrections for Skewness.' Biometrics, Volume 44, Issue 2, 323-338.
Gart, John J. and Nam, Jun-mo. 1990. 'Approximate Interval Estimation of the Difference in Binomial Parameters: Correction for Skewness and Extension to Multiple Tables.' Biometrics, Volume 46, Issue 3, 637-643.
Machin, D., Campbell, M.J., Tan, S.B, and Tan, S.H. 2018. Sample Sizes for Clinical, Laboratory, and Epidemiology Studies, 4th Edition. Wiley Blackwell.
Miettinen, O.S. and Nurminen, M. 1985. 'Comparative analysis of two rates.' Statistics in Medicine 4: 213-226.

This report shows the numeric results of this power study. Notice that the results are shown in blocks of four rows at a time. Each block represents a single design.

## Plots Section

**Plots**




This plot gives a visual presentation to the results in the Numeric Report. We can quickly see the impact on the total cluster count, K, of increasing the cluster size, M.

# Example 2 – Validation using a Previously Validated Procedure

We could not find a validation result in the statistical literature, so we will use a previously validated **PASS** procedure (**Superiority by a Margin Tests for the Ratio of Two Proportions in a Cluster-Randomized Design**) to produce the results for the following example.

We will use a slightly modified version of the settings from Example 1. Specifically we will set K1 = 29, K2 = 29, K3 (control) = 41 and M = 20 and solve for power. The Bonferroni adjustment changes the significance level from 0.025 to 0.0125.

The **Superiority by a Margin Tests for the Ratio of Two Proportions in a Cluster-Randomized Design** procedure is set up as follows.

Design Tab

| | |
|---|---|
| Solve For | **Power** |
| Higher Proportions Are | **Better (H1: P1/P2 > R0)** |
| Alpha | **0.0125** |
| K1 (Clusters in Group 1) | **29** |
| M1 (Average Cluster Size) | **20** |
| K2 (Clusters in Group 2) | **41** |
| M2 (Average Cluster Size) | **M1** |
| R0 (Superiority Ratio) | **1.1** |
| R1 (Actual Ratio) | **1.3** |
| P2 (Group 2 Proportion) | **0.5** |
| ICC (Intracluster Correlation) | **0.002** |

This set of options generates the following report.

**Numeric Results**

Solve For: Power
Groups: 1 = Treatment, 2 = Reference
Test Statistic: Likelihood Score Test (Farrington & Manning)
Hypotheses: H0: P1 / P2 ≤ R0 vs. H1: P1 / P2 > R0

| | Number of Clusters | | | Cluster Size | | Total Sample Size | Proportions | | | Ratio | | Intracluster Correlation | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Power | K1 | K2 | K | M1 | M2 | N | Superiority P1.0 | Actual P1.1 | Reference P2 | Superiority R0 | Actual R1 | ICC | Alpha |
| 0.90098 | 29 | 41 | 70 | 20 | 20 | 1400 | 0.55 | 0.65 | 0.5 | 1.1 | 1.3 | 0.002 | 0.0125 |

The power is computed to be 0.90098.

## 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 | **Power** |
| Higher Proportions Are | **Better (H1: R > R0)** |
| Overall Alpha | **0.025** |
| Bonferroni Adjustment | **Standard Bonferroni** |
| Group Allocation | **Enter the Numbers of Clusters per Group individually** |
| M (Items Per Cluster) | **20** |
| R0 (Superiority Ratio) | **1.1** |
| Control Proportion | **0.5** |
| Control Items Per Cluster | **M** |
| Control Number of Clusters | **41** |
| Set A Number of Groups | **2** |
| Set A Proportion | **0.65** |
| Set A Items Per Cluster | **M** |
| Set A Number of Clusters | **29** |
| Set B Number of Groups | **0** |
| Set C Number of Groups | **0** |
| Set D Number of Groups | **0** |
| More | **Unchecked** |
| ρ (Intracluster Correlation) | **0.002** |

## Output

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

**Numeric Results**

| | |
|---|---|
| Solve For: | Power |
| Test Type: | Farrington and Manning Likelihood Score Test |
| Hypotheses: | H0: Ri ≤ R0 vs. H1: Ri > R0 |
| Number of Groups: | 3 |
| Bonferroni Adjustment: | Standard Bonferroni (Divisor = 2) |

| | | | | | | Ratio | | | Alpha | |
|---|---|---|---|---|---|---|---|---|---|---|
| Comparison | Power | Number of Clusters Ki | Items Per Cluster Mi | Sample Size Ni | Proportion Pi | Superiority R0 | Actual Ri | ICC ρ | Overall | Bonferroni-Adjusted |
| Control | | 41 | 20 | 820 | 0.50 | 1.1 | | 0.002 | | |
| vs A1 | 0.90098 | 29 | 20 | 580 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| vs A2 | 0.90098 | 29 | 20 | 580 | 0.65 | 1.1 | 1.3 | 0.002 | 0.025 | 0.0125 |
| Total | | 99 | | 1980 | | | | | | |

As you can see, the power is 0.90098 for both treatment groups which match the power found in the validation run above. The procedure is validated.