Chapter 606

Multi-Arm Equivalence Tests for the Difference of Treatment and Control Proportions in a Cluster-Randomized Design

Introduction

This module computes power and sample size for multi-arm equivalence tests of the difference between treatment and control proportions when the 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 difference 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 70% 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 equivalence hypotheses need to be tested in this study: whether each new treatment is about the same as the current treatment. Hence, three groups are needed to complete this study of the two new treatments.

Clinicians are willing to adopt a new treatment if it is about as effective as the current treatment. They must determine, however, how much more or less effective the new treatment can be and still be adopted.

Should it be adopted if 65% respond? 68%? 72%? 74%? There are percentages above and below 70% at which the difference between the two treatments is no longer considered ignorable. After thoughtful discussion with several clinicians, it is decided that if a response of between 63% and 77% is achieved, the new treatment will be adopted. The margin of equivalence in this example is 7%.

The developers must design an experiment to test the hypothesis that the response rate of the new treatment is at least 0.63. The statistical hypotheses to be tested are

$$H_0\colon |P_i - P_C| \geq 0.07 \quad \text{vs.} \quad H_1\colon |P_i - P_C| < 0.07$$

where $i = A$ or B.

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 three-arm design consists of three groups: control, treatment A, and treatment B. Two equivalence 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.

Technical Details

Our formulation for cluster-randomized designs comes from Donner and Klar (2000).

Denote a binary (0, 1) observation by Y_{ikj} where *i* is one of *G+1* groups, *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 difference 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.

The *G* equivalence-test hypotheses are

$$H_{0i}\colon P_i - P_C \leq D0.L \;\text{ or }\; P_i - P_C \geq D0.U \quad \text{vs.} \quad H_{1i}\colon D0.L < P_i - P_C < D0.U \quad \text{for } i = 1, 2, \dots, G$$

where $D0.L$ and $D0.U$ are the equivalence limits.

If we define $\delta_i = P_i - P_C$, these are equivalent to

$$H_{0i}\colon \delta_i \leq D0.L \;\text{ or }\; \delta_i \geq D0.U \quad \text{vs.} \quad H_{1i}\colon D0.L < \delta_i < D0.U \quad \text{for } i = 1, 2, \dots, G$$

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 sometimes called the *inflation factor*. The Greek letter ρ 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 ρ 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 TOST z-tests becomes

$$z_L = \frac{\left|\hat{D} - D0.L\right|}{\hat{\sigma}_{\hat{D}}(D0.L)}$$

where

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

$$\hat{\sigma}_{\hat{D}}(\delta_0) = \sqrt{\frac{\tilde{p}_i(1-\tilde{p}_i)F_{i,\rho}}{N_i} + \frac{\tilde{p}_C(1-\tilde{p}_C)F_{C,\rho}}{N_C}}$$

The quantities $\tilde{p}_i$ and $\tilde{p}_C$ are the maximum likelihood estimates constrained by $\tilde{p}_i - \tilde{p}_C = D0.L$.

Test Statistics

Three test statistics are available in this routine. These are

Z-Test (or Chi-Square Test) (Pooled and Unpooled)

This test statistic was first proposed by Karl Pearson in 1900. Although this test is usually expressed directly as a Chi-Square statistic, it is expressed here as a *z* statistic so that it can be more easily used for one-sided hypothesis testing.

Both *pooled* and *unpooled* versions of this test have been discussed in the statistical literature. The pooling refers to the way in which the standard error is estimated. In the pooled version, the two proportions are averaged, and only one proportion is used to estimate the standard error. In the unpooled version, the two proportions are used separately.

The formula for the test statistic is

$$z_i = \frac{\hat{p}_i - \hat{p}_C}{\hat{\sigma}_D}$$

Pooled Version

$$\hat{\sigma}_D = \sqrt{\hat{p}(1-\hat{p})\left(\frac{F_{i,\rho}}{N_i} + \frac{F_{c,\rho}}{N_C}\right)}$$

$$\hat{p} = \frac{N_i \hat{p}_i + N_C \hat{p}_C}{N_i + N_C}$$

Unpooled Version

$$\hat{\sigma}_D = \sqrt{\frac{\hat{p}_i(1-\hat{p}_i)F_{i,\rho}}{N_i} + \frac{\hat{p}_C(1-\hat{p}_C)F_{c,\rho}}{N_C}}$$

Power

The following normal approximation to the binomial is used as presented in Chow et al. (2008).

1. Find the critical value (or values in the case of a two-sided test) using the standard normal distribution. The critical value is that value of *z* that leaves exactly the target value of alpha in the tail.
2. Use the normal approximation to binomial distribution to compute binomial probabilities, compute the power for the pooled and unpooled tests, respectively, using

Pooled: $1 - \beta = \Pr\left(Z < \frac{z_\alpha \sigma_{D,p} + (p_i - p_C)}{\sigma_{D,u}}\right)$ **Unpooled:** $1 - \beta = \Pr\left(Z < \frac{z_\alpha \sigma_{D,u} + (p_i - p_C)}{\sigma_{D,u}}\right)$

where

$$\sigma_{D,u} = \sqrt{\frac{p_i q_i}{N_i / F_{i,\rho}} + \frac{p_C q_C}{N_C F_{c,\rho}}}$$ (unpooled standard error)

$$\sigma_{D,p} = \sqrt{\overline{p}\overline{q}\left(\frac{F_{i,\rho}}{N_i} + \frac{F_{c,\rho}}{N_C}\right)}$$ (pooled standard error)

with $\overline{p} = \frac{N_i p_i + N_C p_C}{N_i + N_C}$ and $\overline{q} = 1 - \overline{p}$

Farrington and Manning's Likelihood Score Test

Farrington and Manning (1990) proposed a test statistic for testing whether the difference is equal to a specified value δ_0. 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 $\tilde{p}_i - \tilde{p}_C = \delta_0$, 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

$$z_{FMD} = \frac{\hat{p}_i - \hat{p}_C - D0.L}{\sqrt{\left(\frac{\tilde{p}_i \tilde{q}_i}{N_i / F_{i,\rho}} + \frac{\tilde{p}_C \tilde{q}_C}{N_C / F_{C,\rho}}\right)}}$$

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

Multiplicity Adjustment

Because *G* TOST z-tests between treatment groups and the control group are run when analyzing the results of this study, most 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 groups, 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 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 investigate the equivalence of two treatments to the standard drug in patients with a specific type of disease. They plan to use the Farrington and Manning likelihood score test to analyze the data.

Historically, the standard treatment has enjoyed a 70% cure rate. The new treatments both reduce the seriousness of certain side effects of the standard treatment. Thus, either of the new treatments will be adopted even if they are found to be equivalent to the standard treatment. The researchers will recommend adoption of the either of the new treatments if they exhibit a cure rate that is within 10% of the standard drug. That is, the margin of equivalence is 0.07. The investigators would like a sample size large enough to find statistical significance at the 0.05 level and the power is 0.80 in each test. Based on similar studies, they estimate the intracluster correlation to be 0.01.

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 for 10 to 30. Since the control group will be used twice, they set the control group allocation ratio to $\sqrt{G} = \sqrt{2} = 1.414$. The two treatment allocation ratios are set to 1.0.

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**
Test Type	**Likelihood Score (Farr. & Mann.)**
Power of Each Test	**0.8**
Overall Alpha	**0.05**
Bonferroni Adjustment	**Standard Bonferroni**
Group Allocation	**Enter Group Allocation Pattern, solve for group numbers of clusters**
M (Items Per Cluster)	**10 20 30**
D0.U (Upper Equivalence Difference)	**0.07**
D0.L (Lower Equivalence Difference)	**-D0.U**
Control Proportion	**0.7**
Control Items Per Cluster	**M**
Control Cluster Allocation	**1.414**
Set A Number of Groups	**2**
Set A Proportion	**0.7**
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)	**0.01**

Output

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

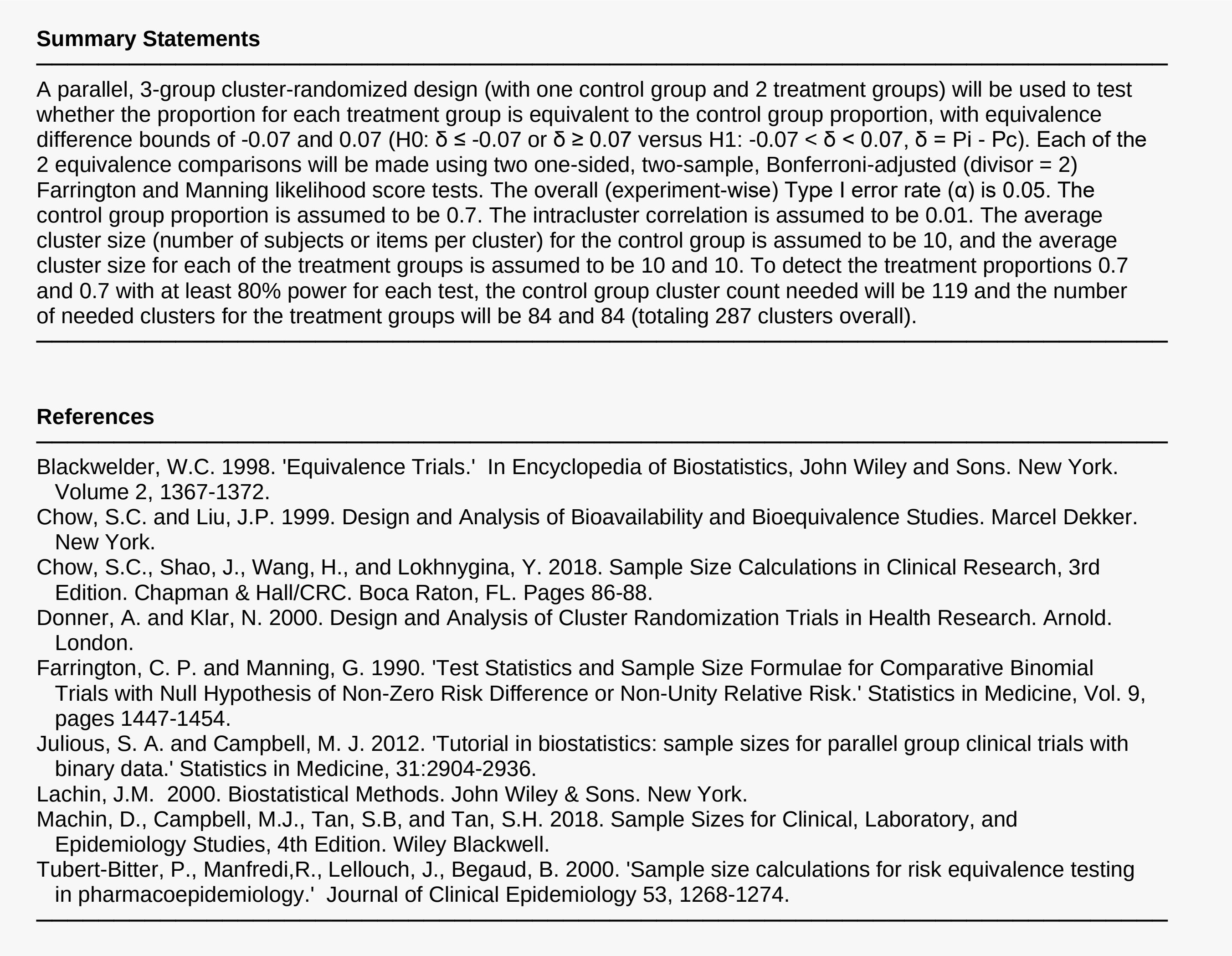
Numeric Reports

Numeric Results

Solve For: Sample Size
Group Allocation: Enter Group Allocation Pattern, solve for group numbers of clusters
Hypothesis: H0: Pi - Pc ≤ D0.L or Pi - Pc ≥ D0.U vs. H1: D0.L < Pi - Pc < D0.U
Test Type: Farrington and Manning Likelihood Score Test
Number of Groups: 3
Bonferroni Adjustment: Standard Bonferroni (Divisor = 2)

	Power		Number of		Items Per	Sample			Equivalence Limits			Alpha	
Comparison	Target	Actual	Clusters Ki	Cluster Allocation	Cluster Mi	Size Ni	Proportion Pi	Difference δi	Lower D0.L	Upper D0.U	ICC ρ	Overall	Bonferroni-Adjusted
Control			119	1.414	10	1190	0.7		-0.07	0.07	0.01		
vs A1	0.8	0.80246	84	1.000	10	840	0.7	0	-0.07	0.07	0.01	0.05	0.025
vs A2	0.8	0.80246	84	1.000	10	840	0.7	0	-0.07	0.07	0.01	0.05	0.025
Total			287			2870							
Control			65	1.414	20	1300	0.7		-0.07	0.07	0.01		
vs A1	0.8	0.80366	46	1.000	20	920	0.7	0	-0.07	0.07	0.01	0.05	0.025
vs A2	0.8	0.80366	46	1.000	20	920	0.7	0	-0.07	0.07	0.01	0.05	0.025
Total			157			3140							
Control			47	1.414	30	1410	0.7		-0.07	0.07	0.01		
vs A1	0.8	0.80135	33	1.000	30	990	0.7	0	-0.07	0.07	0.01	0.05	0.025
vs A2	0.8	0.80135	33	1.000	30	990	0.7	0	-0.07	0.07	0.01	0.05	0.025
Total			113			3390							

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 difference.
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.
δi The difference between the ith group proportion (Pi) and the control group proportion (Pc) at which the power is calculated. The formula is δi = Pi - Pc.
D0.L The lower equivalence difference is the smallest negative difference in treatment and control proportions that still results in the conclusion that they are equivalent.
D0.U The upper equivalence difference is the largest positive difference in treatment and control proportions that still results in the conclusion that they are equivalent.
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 equivalent to the control group proportion, with equivalence difference bounds of -0.07 and 0.07 (H0: δ ≤ -0.07 or δ ≥ 0.07 versus H1: -0.07 < δ < 0.07, δ = Pi - Pc). Each of the 2 equivalence comparisons will be made using two one-sided, two-sample, Bonferroni-adjusted (divisor = 2) Farrington and Manning likelihood score tests. The overall (experiment-wise) Type I error rate (α) is 0.05. The control group proportion is assumed to be 0.7. The intracluster correlation is assumed to be 0.01. 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 0.7 and 0.7 with at least 80% power for each test, the control group cluster count needed will be 119 and the number of needed clusters for the treatment groups will be 84 and 84 (totaling 287 clusters overall).

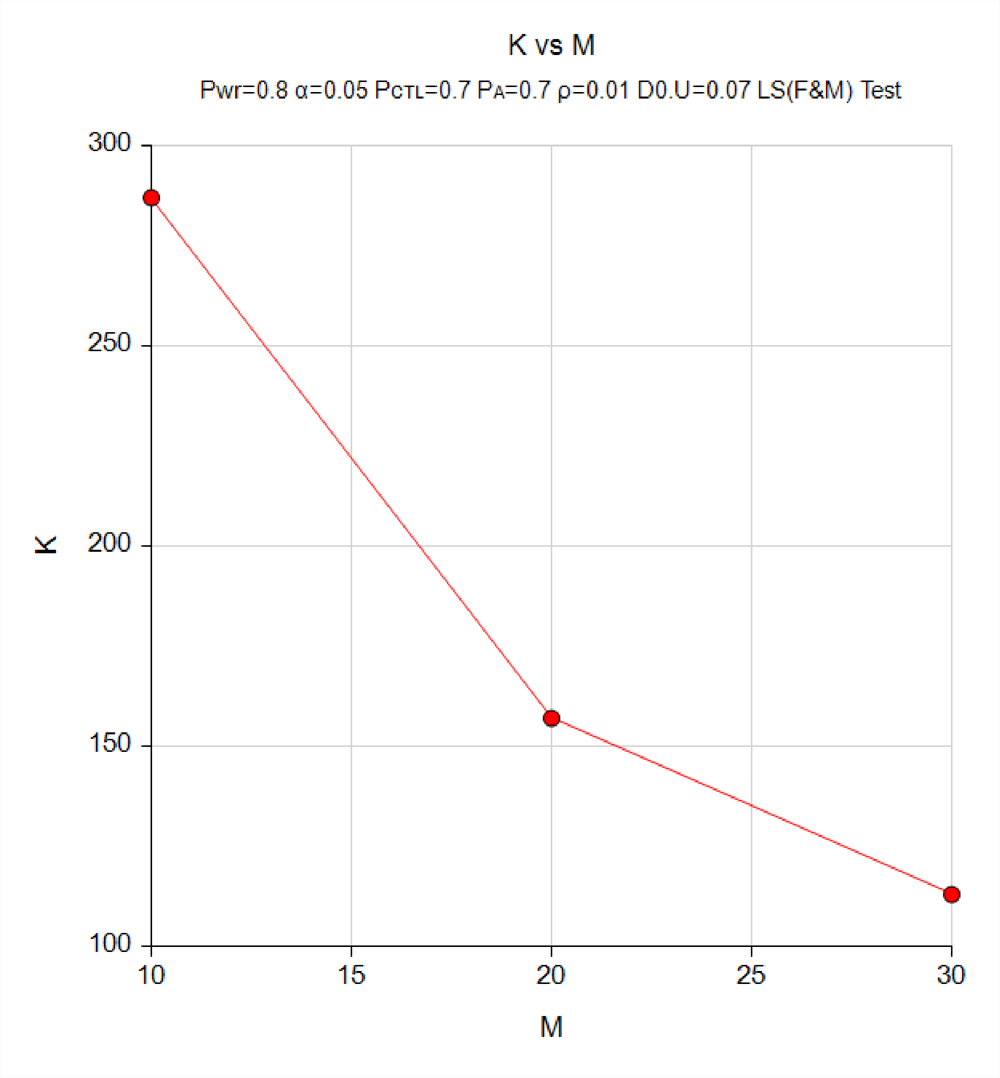
References

Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.
Chow, S.C. and Liu, J.P. 1999. Design and Analysis of Bioavailability and Bioequivalence Studies. Marcel Dekker. New York.
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.
Donner, A. and Klar, N. 2000. Design and Analysis of Cluster Randomization Trials in Health Research. Arnold. London.
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.
Julious, S. A. and Campbell, M. J. 2012. 'Tutorial in biostatistics: sample sizes for parallel group clinical trials with binary data.' Statistics in Medicine, 31:2904-2936.
Lachin, J.M. 2000. Biostatistical Methods. John Wiley & Sons. New York.
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.
Tubert-Bitter, P., Manfredi,R., Lellouch, J., Begaud, B. 2000. 'Sample size calculations for risk equivalence testing in pharmacoepidemiology.' Journal of Clinical Epidemiology 53, 1268-1274.

This report shows the numeric results of this sample size 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 (**Equivalence Tests for the Difference of Two Proportions in a Cluster-Randomized Design**) to produce the results for the following example.

We will use the settings similar to those of Example 1 specifically when M = 30. In this case, the number of clusters allocated to the control group was 47 and to the treatment groups was 33 in each. The Bonferroni adjustment changes the significance level from 0.05 to 0.025.

The **Equivalence Tests for the Difference of Two Proportions in a Cluster-Randomized Design** procedure is set up as follows.

```
Design Tab

Solve For ..........................................Power
Test Type...........................................Likelihood Score (Farr. & Mann.)
Alpha...............................................0.025
K1 (Clusters in Group 1) ...........................33
M1 (Average Cluster Size)...........................30
K2 (Clusters in Group 2) ...........................47
M2 (Average Cluster Size)...........................30
Input Type..........................................Differences
D0.U (Upper Equivalence Difference).................0.07
D0.L (Lower Equivalence Difference) ................-D0.U
D1 (Actual Difference)..............................0
P2 (Group 2 Proportion).............................0.7
ICC (Intracluster Correlation)......................0.01
```

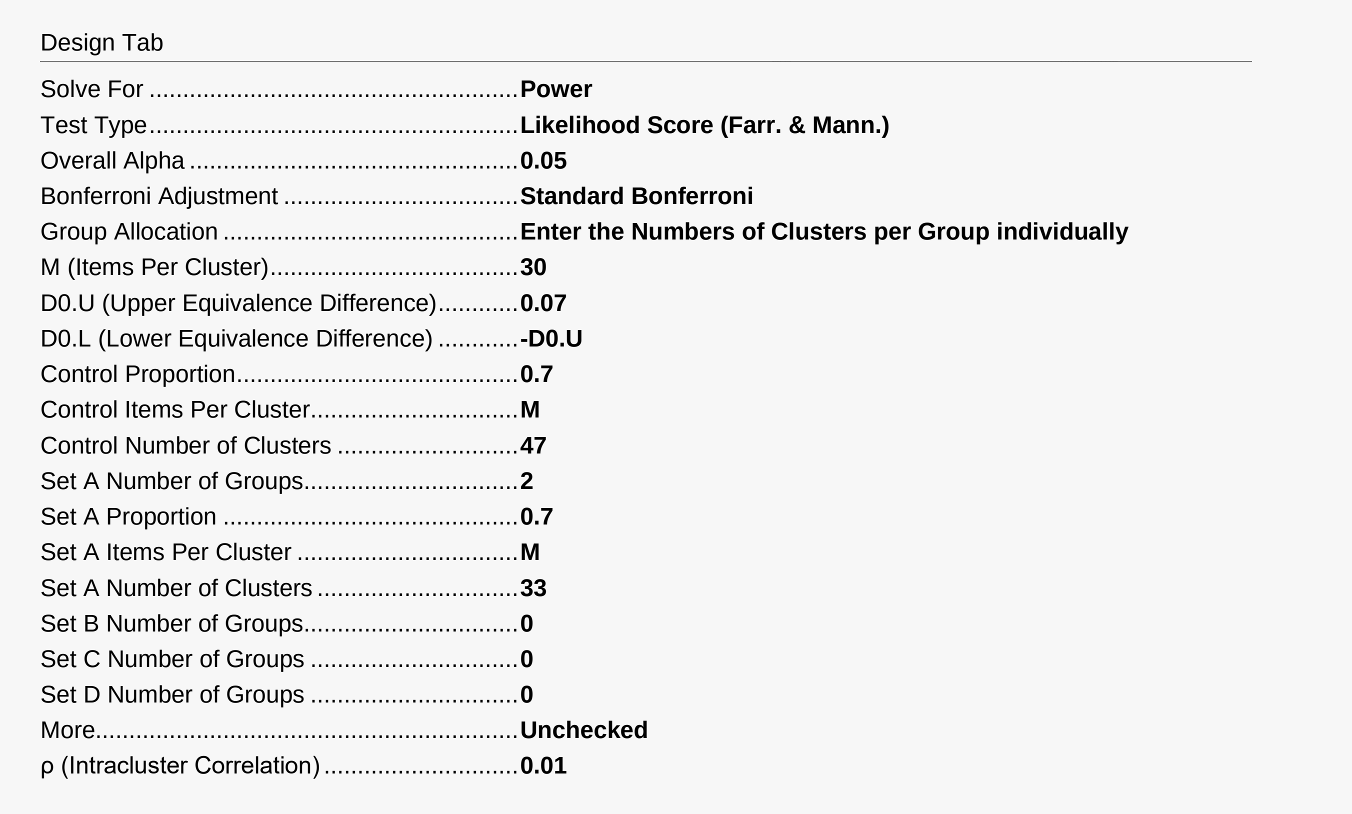
This set of options generates the following report.

```
Numeric Results

Solve For:       Power
Groups:          1 = Treatment, 2 = Reference
Test Statistic:  Likelihood Score Test (Farrington & Manning)
Hypotheses:      H0: P1 - P2 ≤ D0.L or P1 - P2 ≥ D0.U   vs.   H1: D0.L < P1 - P2 < D0.U

                                Average                            Proportion                          Difference
               Number of        Cluster     Total    ---------------------------------------   --------------------------
               Clusters          Size       Sample   Equivalence                                Equivalence                Intracluster
            ---------------   ----------    Size     -------------   Actual    Reference        -------------   Actual     Correlation
Power        K1   K2    K      M1    M2        N     P1.L | P1.U       P1.1           P2        D0.L | D0.U         D1             ICC    Alpha
0.80135      33   47   80      30    30     2400     0.63 | 0.77        0.7          0.7       -0.07 | 0.07          0            0.01    0.025
```

The power is computed to be 0.80135.

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.

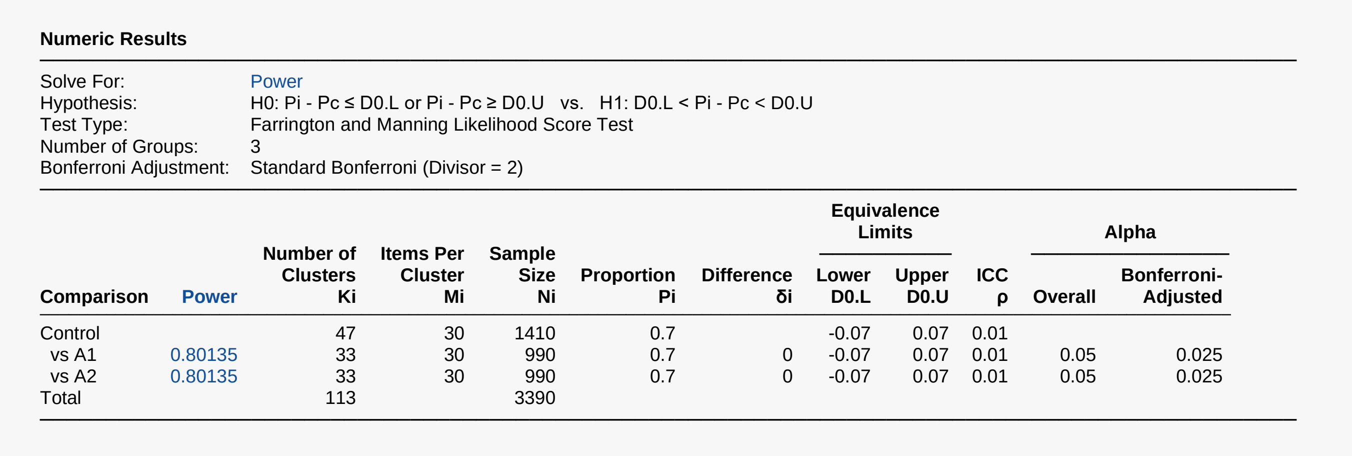


Design Tab

Solve For .... **Power**
Test Type.. **Likelihood Score (Farr. & Mann.)**
Overall Alpha **0.05**
Bonferroni Adjustment .... **Standard Bonferroni**
Group Allocation .... **Enter the Numbers of Clusters per Group individually**
M (Items Per Cluster)..................................... **30**
D0.U (Upper Equivalence Difference)............ **0.07**
D0.L (Lower Equivalence Difference) .... **-D0.U**
Control Proportion.. **0.7**
Control Items Per Cluster............................... **M**
Control Number of Clusters **47**
Set A Number of Groups................................ **2**
Set A Proportion **0.7**
Set A Items Per Cluster .... **M**
Set A Number of Clusters **33**
Set B Number of Groups................................ **0**
Set C Number of Groups **0**
Set D Number of Groups **0**
More... **Unchecked**
ρ (Intracluster Correlation) **0.01**

Output

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



```
Numeric Results

Solve For:               Power
Hypothesis:              H0: Pi - Pc ≤ D0.L or Pi - Pc ≥ D0.U   vs.   H1: D0.L < Pi - Pc < D0.U
Test Type:               Farrington and Manning Likelihood Score Test
Number of Groups:        3
Bonferroni Adjustment:   Standard Bonferroni (Divisor = 2)

                                                                             Equivalence
                                                                               Limits                     Alpha
                         Number of  Items Per  Sample                                       ------------------------
                          Clusters    Cluster    Size  Proportion  Difference  Lower  Upper   ICC              Bonferroni-
Comparison    Power             Ki         Mi      Ni          Pi          δi   D0.L   D0.U     ρ  Overall      Adjusted

Control                         47         30    1410         0.7               -0.07   0.07  0.01
  vs A1      0.80135            33         30     990         0.7           0   -0.07   0.07  0.01     0.05         0.025
  vs A2      0.80135            33         30     990         0.7           0   -0.07   0.07  0.01     0.05         0.025
Total                          113               3390
```

As you can see, the power is 0.80135 for both treatment groups which match the power found in the validation run above. The procedure is validated.