

## Chapter 241

# Equivalence Tests for the Ratio of Two Proportions in a Cluster-Randomized Design

## Introduction

This module provides power analysis and sample size calculation for equivalence tests of the ratio in two-sample, cluster-randomized designs in which the outcome is binary.

## 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 ratio of 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 superiority by a margin with two proportions using the ratio can be used here.

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

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

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

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

## Equivalence Tests for the Ratio of Two Proportions in a Cluster-Randomized Design

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 formula for the Farrington and Manning Likelihood Score Test that was used in comparing two proportions (see Chapter 214, “Equivalence Tests for the Ratio of 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.

## Example 1 – Finding Power

A study is being designed to establish the equivalence of a new treatment compared to the current treatment. Historically, the standard treatment has enjoyed a 60% cure rate. The new treatment reduces the seriousness of certain side effects that occur with the standard treatment. Thus, the new treatment will be adopted even if it is slightly less effective than the standard treatment. The researchers will recommend adoption of the new treatment if the rate ratio of treatment to control is between 0.75 and 1.25.

The researchers will recruit patients from various hospitals. All patients at a particular hospital will receive the same treatment. They anticipate enlisting an average of 50 patients per hospital. Based on similar studies, they estimate the intracluster 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 two, one-sided tests proposed by Farrington and Manning when the number of clusters per groups ranges from 2 to 10. They want to investigate the behavior of this test when the actual cure rate of the new treatment ranges from 60% to 66% (rate ratio = 1.0 to 1.1). The significance level will be 0.05.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Power</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 (Average Cluster Size) .....	<b>50</b>
K2 (Clusters in Group 2) .....	<b>K1</b>
M2 (Average Cluster Size) .....	<b>M1</b>
R0.U (Upper Equivalence Ratio) .....	<b>1.25</b>
R0.L (Lower Equivalence Ratio) .....	<b>0.75</b>
R1 (Actual Ratio) .....	<b>1.0 1.05 1.1</b>
P2 (Group 2 Proportion) .....	<b>0.6</b>
ICC (Intracluster Correlation) .....	<b>0.002</b>

## Equivalence Tests for the Ratio of Two Proportions in a Cluster-Randomized Design

## Output

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

## Numeric Reports

## Numeric Results

Solve For: **Power**  
 Groups: 1 = Treatment, 2 = Reference  
 Test Statistic: Likelihood Score Test (Farrington & Manning)  
 Hypotheses:  $H_0: P_1 / P_2 \leq R_{0.L} \text{ or } P_1 / P_2 \geq R_{0.U}$  vs.  $H_1: R_{0.L} < P_1 / P_2 < R_{0.U}$

Power	Number of Clusters			Average Cluster Size		Total Sample Size N	Proportion				Ratio		Intraclass Correlation ICC	Alpha	
							Equivalence		Actual P1.1	Reference P2	Equivalence				Actual R1
	P1.L   P1.U		R0.L   R0.U												
0.32704	2	2	4	50	50	200	0.45   0.75		0.60	0.6	0.75   1.25		1.00	0.002	0.05
0.77694	4	4	8	50	50	400	0.45   0.75		0.60	0.6	0.75   1.25		1.00	0.002	0.05
0.92712	6	6	12	50	50	600	0.45   0.75		0.60	0.6	0.75   1.25		1.00	0.002	0.05
0.97630	8	8	16	50	50	800	0.45   0.75		0.60	0.6	0.75   1.25		1.00	0.002	0.05
0.99240	10	10	20	50	50	1000	0.45   0.75		0.60	0.6	0.75   1.25		1.00	0.002	0.05
0.31030	2	2	4	50	50	200	0.45   0.75		0.63	0.6	0.75   1.25		1.05	0.002	0.05
0.65767	4	4	8	50	50	400	0.45   0.75		0.63	0.6	0.75   1.25		1.05	0.002	0.05
0.81499	6	6	12	50	50	600	0.45   0.75		0.63	0.6	0.75   1.25		1.05	0.002	0.05
0.90181	8	8	16	50	50	800	0.45   0.75		0.63	0.6	0.75   1.25		1.05	0.002	0.05
0.94937	10	10	20	50	50	1000	0.45   0.75		0.63	0.6	0.75   1.25		1.05	0.002	0.05
0.24921	2	2	4	50	50	200	0.45   0.75		0.66	0.6	0.75   1.25		1.10	0.002	0.05
0.46869	4	4	8	50	50	400	0.45   0.75		0.66	0.6	0.75   1.25		1.10	0.002	0.05
0.60903	6	6	12	50	50	600	0.45   0.75		0.66	0.6	0.75   1.25		1.10	0.002	0.05
0.71705	8	8	16	50	50	800	0.45   0.75		0.66	0.6	0.75   1.25		1.10	0.002	0.05
0.79842	10	10	20	50	50	1000	0.45   0.75		0.66	0.6	0.75   1.25		1.10	0.002	0.05

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
K1, K2, and K	The number of clusters in groups 1, 2, and both, respectively.
M1 and M2	The average number of items (subjects) per cluster in groups 1 and 2, respectively.
N	The total sample size for the study. $N = (K_1 \times M_1) + (K_2 \times M_2)$ .
P1.L	The smallest proportion for group 1 (treatment group) that still results in the conclusion of equivalence.
P1.U	The largest proportion for group 1 (treatment group) that still results in the conclusion of equivalence.
P1.1	The actual value of the proportion for group 1. This is the value at which the power is calculated.
P2	The proportion for group 2, the standard, reference, baseline, or control group.
R0.L	The smallest ratio that still results in the conclusion of equivalence. $R_{0.L} = P_{1.L}/P_2$ .
R0.U	The largest ratio that still results in the conclusion of equivalence. $R_{0.U} = P_{1.U}/P_2$ .
R1	The actual ratio at which the power is calculated. $R_1 = P_{1.1}/P_2$ .
ICC	The intraclass correlation. This is the correlation between any two subjects within a cluster.
Alpha	The probability of rejecting a true null hypothesis.

## Summary Statements

A parallel two-group cluster-randomized design will be used to test whether the Group 1 (treatment) proportion (P1) is equivalent to the Group 2 (reference) proportion (P2), with ratio equivalence bounds of 0.75 and 1.25 ( $H_0: P_1 / P_2 \leq 0.75 \text{ or } P_1 / P_2 \geq 1.25$  versus  $H_1: 0.75 < P_1 / P_2 < 1.25$ ). The comparison will be made using two one-sided Likelihood Score Tests (Farrington & Manning), with an overall Type I error rate ( $\alpha$ ) of 0.05. The reference group proportion (P2) is assumed to be 0.6. The intraclass correlation is assumed to be 0.002. To detect a proportion ratio (P1 / P2) of 1 (or P1 of 0.6), with 2 clusters of 50 subjects per cluster in Group 1 and 2 clusters of 50 subjects per cluster in Group 2, the power is 0.32704.

## Equivalence Tests for the Ratio of Two Proportions in a Cluster-Randomized Design

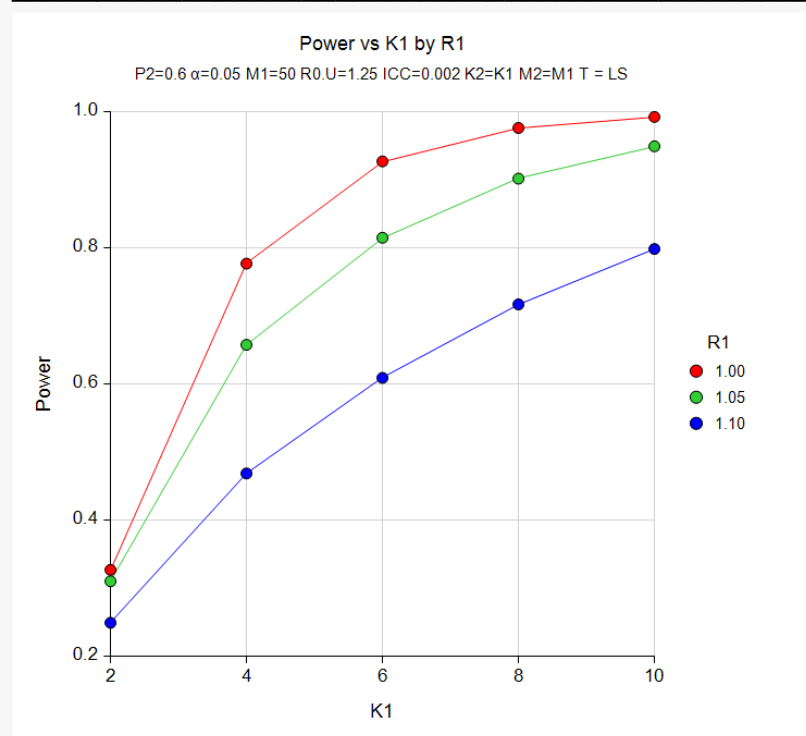
## References

- 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.
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- 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.
- Miettinen, O.S. and Nurminen, M. 1985. 'Comparative analysis of two rates.' Statistics in Medicine 4: 213-226.

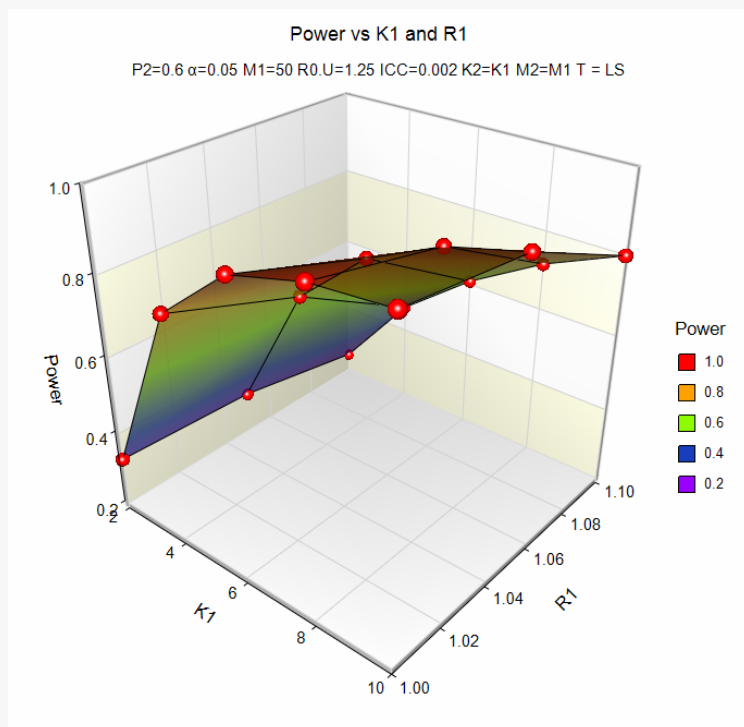
This report shows the values of each of the parameters, one scenario per row. The total number of items sampled in group 1 is  $N1 = K1 \times M1$ . The total number of items sampled in group 2 is  $N2 = K2 \times M2$ .

## Plots Section

## Plots



## Equivalence Tests for the Ratio of Two Proportions in a Cluster-Randomized Design



The values from the table are displayed on the above plots. These plots give a quick look at the sample size that will be required for various values of  $R1$ .

## 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 R1 when the target power is set to 0.80.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For ..... **Sample Size (K1)**  
 Test Type..... **Likelihood Score (Farr. & Mann.)**  
 Power..... **0.80**  
 Alpha..... **0.05**  
 M1 (Average Cluster Size)..... **50**  
 K2 (Clusters in Group 2)..... **K1**  
 M2 (Average Cluster Size)..... **M1**  
 R0.U (Upper Equivalence Ratio)..... **1.25**  
 R0.L (Lower Equivalence Ratio) ..... **0.75**  
 R1 (Actual Ratio) ..... **1.0 1.05 1.1**  
 P2 (Group 2 Proportion)..... **0.6**  
 ICC (Intraclass Correlation)..... **0.002**

### Output

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

#### Numeric Results

Solve For: [Sample Size \(K1\)](#)  
 Groups: 1 = Treatment, 2 = Reference  
 Test Statistic: Likelihood Score Test (Farrington & Manning)  
 Hypotheses:  $H_0: P_1 / P_2 \leq R_{0.L} \text{ or } P_1 / P_2 \geq R_{0.U}$  vs.  $H_1: R_{0.L} < P_1 / P_2 < R_{0.U}$

Power	Number of Clusters			Average Cluster Size		Total Sample Size N	Proportion			Ratio		Intraclass Correlation ICC	Alpha
	K1	K2	K	M1	M2		Equivalence P1.L   P1.U	Actual P1.1	Reference P2	Equivalence R0.L   R0.U	Actual R1		
0.87247	5	5	10	50	50	500	0.45   0.75	0.60	0.6	0.75   1.25	1.00	0.002	0.05
0.81499	6	6	12	50	50	600	0.45   0.75	0.63	0.6	0.75   1.25	1.05	0.002	0.05
0.83073	11	11	22	50	50	1100	0.45   0.75	0.66	0.6	0.75   1.25	1.10	0.002	0.05

The required sample size depends a great deal on the value of R1. The researchers should spend time determining the most appropriate value for R1.

## Example 3 – Finding Sample Size (Individuals within Clusters)

Continuing with the scenario given in Example 2, the researchers want to determine the number of individuals that they'll need to recruit in each hospital if they can enroll only 5 hospitals vs 10 in each group for each value of R1 when the target power is set to 0.80.

### Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

#### Design Tab

Solve For .....	<b>Sample Size (M1)</b>
Test Type .....	<b>Likelihood Score (Farr. &amp; Mann.)</b>
Power .....	<b>0.80</b>
Alpha .....	<b>0.05</b>
K1 (Clusters in Group 1) .....	<b>5 10</b>
K2 (Clusters in Group 2) .....	<b>K1</b>
M2 (Average Cluster Size) .....	<b>M1</b>
R0.U (Upper Equivalence Ratio) .....	<b>1.25</b>
R0.L (Lower Equivalence Ratio) .....	<b>0.75</b>
R1 (Actual Ratio) .....	<b>1.0 1.05 1.1</b>
P2 (Group 2 Proportion) .....	<b>0.6</b>
ICC (Intraclass Correlation) .....	<b>0.002</b>



## Equivalence Tests for the Ratio of Two Proportions in a Cluster-Randomized Design

## Output

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

## Numeric Results

Solve For: [Sample Size \(M1\)](#)  
 Groups: 1 = Treatment, 2 = Reference  
 Test Statistic: Likelihood Score Test (Farrington & Manning)  
 Hypotheses:  $H_0: P_1 / P_2 \leq R_{0.L} \text{ or } P_1 / P_2 \geq R_{0.U}$  vs.  $H_1: R_{0.L} < P_1 / P_2 < R_{0.U}$

Power	Number of Clusters			Average Cluster Size		Total Sample Size N	Proportion				Ratio		Intraclass Correlation ICC	Alpha		
							Equivalence		Actual P1.1	Reference P2	Equivalence				Actual R1	
	P1.L   P1.U	P1.U	R0.L   R0.U	R0.U												
0.80732	5	5	10	42	42	420	0.45   0.75		0.60		0.6	0.75   1.25		1.00	0.002	0.05
0.80397	10	10	20	20	20	400	0.45   0.75		0.60		0.6	0.75   1.25		1.00	0.002	0.05
0.80349	5	5	10	59	59	590	0.45   0.75		0.63		0.6	0.75   1.25		1.05	0.002	0.05
0.80523	10	10	20	28	28	560	0.45   0.75		0.63		0.6	0.75   1.25		1.05	0.002	0.05
0.80063	5	5	10	112	112	1120	0.45   0.75		0.66		0.6	0.75   1.25		1.10	0.002	0.05
0.80466	10	10	20	51	51	1020	0.45   0.75		0.66		0.6	0.75   1.25		1.10	0.002	0.05

If they can enroll 10 hospitals, then they need to recruit between 20 and 51 patients at each, depending on the actual cure rate ratio. If they can only enroll 5 hospitals, then they'll need to recruit many more patients... between 42 and 112.

## Example 4 – Validation

We could not find an example of this type of analysis in the literature. Therefore, we will validate the procedure by comparing the results to those computed by the “Equivalence Tests for the Ratio of Two Proportions” procedure since both should give identical results for the same sample sizes when the ICC is set to zero. We ran the case when  $N_1 = N_2 = 200$ ,  $P_2 = 0.6$ ,  $R_{0.U} = 1.2$ ,  $R_{0.L} = 1/R_{0.U}$ ,  $R_1 = 1$ , and  $\alpha = 0.05$ . In this procedure, set  $M_1 = 1$  and set  $K_1 = 200$ . The Equivalence Tests for the Ratio of Two Proportions procedure calculates the power to be 0.43259 for the Likelihood Score (Farrington & Manning) test.

## Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4** 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.)**  
 Alpha..... **0.05**  
 K1 (Clusters in Group 1)..... **200**  
 M1 (Average Cluster Size)..... **1**  
 K2 (Clusters in Group 2)..... **K1**  
 M2 (Average Cluster Size)..... **M1**  
 R0.U (Upper Equivalence Ratio)..... **1.2**  
 R0.L (Lower Equivalence Ratio)..... **1/R0.U**  
 R1 (Actual Ratio) ..... **1.0**  
 P2 (Group 2 Proportion)..... **0.6**  
 ICC (Intraclass Correlation)..... **0.0**

## Output

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

### Numeric Results

Solve For: **Power**  
 Groups: 1 = Treatment, 2 = Reference  
 Test Statistic: Likelihood Score Test (Farrington & Manning)  
 Hypotheses:  $H_0: P_1 / P_2 \leq R_{0.L} \text{ or } P_1 / P_2 \geq R_{0.U}$  vs.  $H_1: R_{0.L} < P_1 / P_2 < R_{0.U}$

Power	Number of Clusters			Average Cluster Size		Total Sample Size N	Proportion			Ratio		Intraclass Correlation ICC	Alpha		
	K1	K2	K	M1	M2		Equivalence		Actual P1.1	Reference P2	Equivalence			Actual R1	
							P1.L   P1.U				R0.L   R0.U				
0.43259	200	200	400	1	1	400	0.5   0.72	0.6	0.6	0.833   1.2	1	0	0.05		

The power computed by this procedure is also 0.43259 when ICC = 0.