Chapter 236

Non-Inferiority Tests for the Ratio of Two Proportions in a Cluster-Randomized Design

Introduction

This module provides power analysis and sample size calculation for non-inferiority 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, ..., K_g is a cluster within group g, and m = 1, 2, ..., 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

$$\sigma_{C,g}^2 = \frac{p_g(1 - p_g)\big(1 + (m_g - 1)\rho\big)}{k_g m_g}$$

$$= \sigma_{S,g}^2\big[1 + (m_g - 1)\rho\big]$$

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

The factor $[1 + (m_g - 1)\rho]$ is 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 formula for the Farrington and Manning Likelihood Score Test that was used in comparing two proportions (see Chapter 211, "Non-Inferiority 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.

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 study the effectiveness of a new 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 ratio of the new treatment to the old treatment is at least 0.92.

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 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 one-sided Farrington and Manning test at group cluster sizes ranging from 2 to 10 for detecting a ratio of 0.92 when the actual cure rate ratio ranges from 1 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 ....**Power**
Higher Proportions Are ....**Better (H1: P1/P2 > R0)**
Alpha...**0.05**
K1 (Clusters in Group 1) **2 4 6 8 10**
M1 (Average Cluster Size)..............................**100**
K2 (Clusters in Group 2) **K1**
M2 (Average Cluster Size)..............................**M1**
R0 (Non-Inferiority Ratio)..............................**0.92**
R1 (Actual Ratio) ....**1 to 1.1 by 0.02**
P2 (Group 2 Proportion).................................**0.6**
ICC (Intracluster Correlation).........................**0.002**

Output

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

Numeric Reports

Numeric Results
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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
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| | Number of Clusters | | | Cluster Size | | Total Sample Size | Proportions | | | Ratio | | Intracluster Correlation | |
Power	K1	K2	K	M1	M2	N	Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority R0	Actual R1	ICC	Alpha
0.23776	2	2	4	100	100	400	0.552	0.600	0.6	0.92	1.00	0.002	0.05
0.37161	4	4	8	100	100	800	0.552	0.600	0.6	0.92	1.00	0.002	0.05
0.48744	6	6	12	100	100	1200	0.552	0.600	0.6	0.92	1.00	0.002	0.05
0.58634	8	8	16	100	100	1600	0.552	0.600	0.6	0.92	1.00	0.002	0.05
0.66934	10	10	20	100	100	2000	0.552	0.600	0.6	0.92	1.00	0.002	0.05
0.31627	2	2	4	100	100	400	0.552	0.612	0.6	0.92	1.02	0.002	0.05
0.50224	4	4	8	100	100	800	0.552	0.612	0.6	0.92	1.02	0.002	0.05
0.64685	6	6	12	100	100	1200	0.552	0.612	0.6	0.92	1.02	0.002	0.05
0.75483	8	8	16	100	100	1600	0.552	0.612	0.6	0.92	1.02	0.002	0.05
0.83285	10	10	20	100	100	2000	0.552	0.612	0.6	0.92	1.02	0.002	0.05
0.40466	2	2	4	100	100	400	0.552	0.624	0.6	0.92	1.04	0.002	0.05
0.63348	4	4	8	100	100	800	0.552	0.624	0.6	0.92	1.04	0.002	0.05
0.78465	6	6	12	100	100	1200	0.552	0.624	0.6	0.92	1.04	0.002	0.05
0.87794	8	8	16	100	100	1600	0.552	0.624	0.6	0.92	1.04	0.002	0.05
0.93276	10	10	20	100	100	2000	0.552	0.624	0.6	0.92	1.04	0.002	0.05
0.49891	2	2	4	100	100	400	0.552	0.636	0.6	0.92	1.06	0.002	0.05
0.75149	4	4	8	100	100	800	0.552	0.636	0.6	0.92	1.06	0.002	0.05
0.88540	6	6	12	100	100	1200	0.552	0.636	0.6	0.92	1.06	0.002	0.05
0.94986	8	8	16	100	100	1600	0.552	0.636	0.6	0.92	1.06	0.002	0.05
0.97893	10	10	20	100	100	2000	0.552	0.636	0.6	0.92	1.06	0.002	0.05
0.59400	2	2	4	100	100	400	0.552	0.648	0.6	0.92	1.08	0.002	0.05
0.84620	4	4	8	100	100	800	0.552	0.648	0.6	0.92	1.08	0.002	0.05
0.94745	6	6	12	100	100	1200	0.552	0.648	0.6	0.92	1.08	0.002	0.05
0.98328	8	8	16	100	100	1600	0.552	0.648	0.6	0.92	1.08	0.002	0.05
0.99495	10	10	20	100	100	2000	0.552	0.648	0.6	0.92	1.08	0.002	0.05
0.68464	2	2	4	100	100	400	0.552	0.660	0.6	0.92	1.10	0.002	0.05
0.91383	4	4	8	100	100	800	0.552	0.660	0.6	0.92	1.10	0.002	0.05
0.97948	6	6	12	100	100	1200	0.552	0.660	0.6	0.92	1.10	0.002	0.05
0.99554	8	8	16	100	100	1600	0.552	0.660	0.6	0.92	1.10	0.002	0.05
0.99909	10	10	20	100	100	2000	0.552	0.660	0.6	0.92	1.10	0.002	0.05

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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 number of subjects in the study. N = (K1 x M1) + (K2 x M2).
P1.0   The non-inferiority limit for the group 1 proportion.
P1.1   The actual group 1 proportion assumed by the alternative hypothesis. This is the value at which the power is
                    calculated.
P2   The proportion for group 2, the standard, reference, baseline, or control group.
R0   The non-inferiority ratio. This is the most the proportion ratio of P1 and P2 can be from one for which group 1
                    will be considered non-inferior to group 2.
R1   The actual proportion ratio at which the power is calculated. R1 = P1.1 / P2.
ICC   The intracluster correlation. This may be interpreted as the correlation between any two observations in the
                    same cluster.
Alpha   The probability of rejecting a true null hypothesis.

Summary Statements

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A parallel two-group cluster-randomized design will be used to test whether the Group 1 (treatment) proportion (P1) is non-inferior to the Group 2 (reference) proportion (P2), with a non-inferiority ratio of 0.92 (H0: P1 / P2 ≤ 0.92 versus H1: P1 / P2 > 0.92). The comparison will be made using a one-sided Likelihood Score Test (Farrington & Manning) based on the proportion ratio (P1 / P2), with a Type I error rate (α) of 0.05. The reference group proportion (P2) is assumed to be 0.6. The intracluster 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 100 subjects per cluster in Group 1 and 2 clusters of 100 subjects per cluster in Group 2, the power is 0.23776.

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References

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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.

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.

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.

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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 x M1. The total number of items sampled in group 2 is N2 = K2 x M2.

Plots Section

Plots

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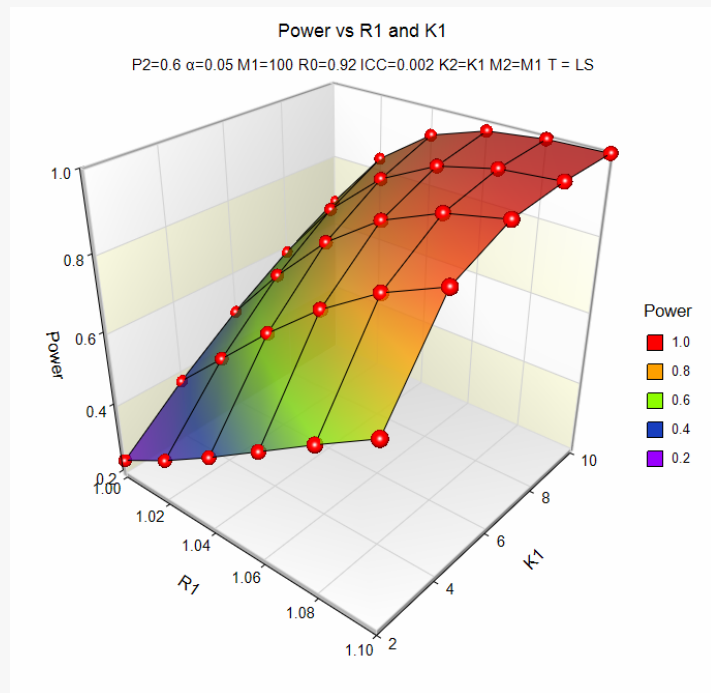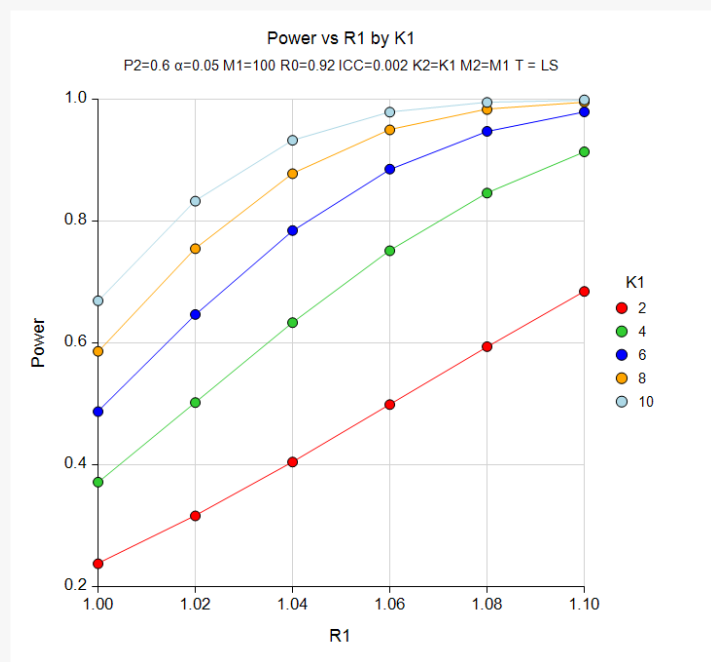
The values from the table are displayed on the above plots. These plots give a quick look at the sample sizes that will be required for various values of R1.

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)**

Higher Proportions Are ....**Better (H1: P1/P2 > R0)**

Power...**0.80**

Alpha..**0.05**

M1 (Average Cluster Size)..............................**100**

K2 (Clusters in Group 2) **K1**

M2 (Average Cluster Size)..............................**M1**

R0 (Non-Inferiority Ratio)..............................**0.92**

R1 (Actual Ratio) ....**1 to 1.1 by 0.02**

P2 (Group 2 Proportion).................................**0.6**

ICC (Intracluster 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: 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	Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority R0	Actual R1	ICC	Alpha
0.81761	15	15	30	100	100	3000	0.552	0.600	0.6	0.92	1.00	0.002	0.05
0.83285	10	10	20	100	100	2000	0.552	0.612	0.6	0.92	1.02	0.002	0.05
0.83722	7	7	14	100	100	1400	0.552	0.624	0.6	0.92	1.04	0.002	0.05
0.82995	5	5	10	100	100	1000	0.552	0.636	0.6	0.92	1.06	0.002	0.05
0.84620	4	4	8	100	100	800	0.552	0.648	0.6	0.92	1.08	0.002	0.05
0.83156	3	3	6	100	100	600	0.552	0.660	0.6	0.92	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 the Sample Size (Individuals within Clusters)

An agency would like to show the proportion of success of a new treatment is no less than that of the current treatment. Thirty doctors are available for the study. Fifteen will be randomly chosen to be trained to administer the new treatment. The remaining fifteen will continue to administer the current treatment. The new treatment will be considered non-inferior if the proportion of success is at least 90% of the current treatment success. The agency would like to know the number of patients that need to be treated by each doctor to achieve 80% power for the non-inferiority test. Various values for the intracluster correlation coefficient will be used since its true value is unknown. It is expected that the two treatments will have a success rate near 0.65. Alpha is set at 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 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 ....**Sample Size (M1)**
Higher Proportions Are ....**Better (H1: P1/P2 > R0)**
Power..**0.80**
Alpha...**0.05**
K1 (Clusters in Group 1) **15**
K2 (Clusters in Group 2) **K1**
M2 (Average Cluster Size)............................**M1**
R0 (Non-Inferiority Ratio)..............................**0.90**
R1 (Actual Ratio) **1.0**
P2 (Group 2 Proportion)................................**0.65**
ICC (Intracluster Correlation).......................**0.001 to 0.01 by 0.001**

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: 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	Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority R0	Actual R1	ICC	Alpha
0.80064	15	15	30	42	42	1260	0.585	0.65	0.65	0.9	1	0.001	0.05
0.80210	15	15	30	44	44	1320	0.585	0.65	0.65	0.9	1	0.002	0.05
0.80221	15	15	30	46	46	1380	0.585	0.65	0.65	0.9	1	0.003	0.05
0.80114	15	15	30	48	48	1440	0.585	0.65	0.65	0.9	1	0.004	0.05
0.80453	15	15	30	51	51	1530	0.585	0.65	0.65	0.9	1	0.005	0.05
0.80108	15	15	30	53	53	1590	0.585	0.65	0.65	0.9	1	0.006	0.05
0.80139	15	15	30	56	56	1680	0.585	0.65	0.65	0.9	1	0.007	0.05
0.80025	15	15	30	59	59	1770	0.585	0.65	0.65	0.9	1	0.008	0.05
0.80142	15	15	30	63	63	1890	0.585	0.65	0.65	0.9	1	0.009	0.05
0.80078	15	15	30	67	67	2010	0.585	0.65	0.65	0.9	1	0.010	0.05

Plots
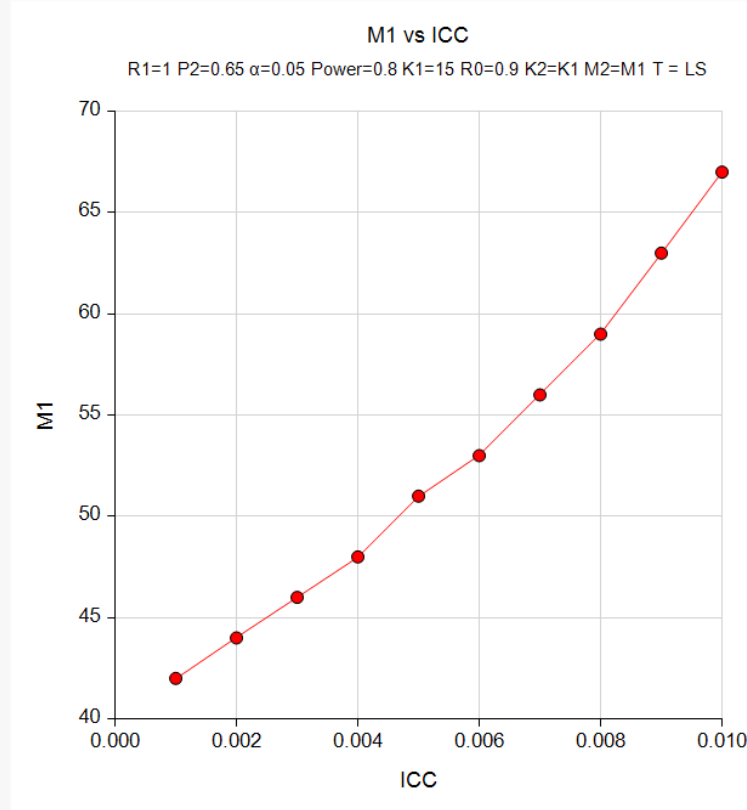
The number of patients that should be seen by each doctor ranges from 42 to 67, depending on the intracluster correlation coefficient.

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.