Chapter 235

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

Introduction

This module provides power analysis and sample size calculation for non-inferiority tests of the difference 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 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

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

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 $\left[1+\left(m_g-1\right)\rho\right]$ 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 formulas that were used in comparing two proportions (see Chapter 210, “Non-Inferiority 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.

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 it has a cure rate of at least 55%. That is, the margin of inferiority is -5%.

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 when the non-inferiority difference is -0.05 and the actual cure rate of the new treatment ranges from 60% to 66%. 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 > D0)**
Test Type	**Likelihood Score (Farr. & Mann.)**
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**
Input Type	**Differences**
D0 (Non-Inferiority Difference)	**-0.05**
D1 (Actual Difference)	**0 0.02 0.04 0.06**
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

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

	Number of Clusters			Cluster Size		Total Sample Size	Proportions			Difference		Intracluster Correlation	
Power	K1	K2	K	M1	M2	N	Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority D0	Actual D1	ICC	Alpha
0.23867	2	2	4	100	100	400	0.55	0.60	0.6	-0.05	0.00	0.002	0.05
0.37284	4	4	8	100	100	800	0.55	0.60	0.6	-0.05	0.00	0.002	0.05
0.48884	6	6	12	100	100	1200	0.55	0.60	0.6	-0.05	0.00	0.002	0.05
0.58780	8	8	16	100	100	1600	0.55	0.60	0.6	-0.05	0.00	0.002	0.05
0.67076	10	10	20	100	100	2000	0.55	0.60	0.6	-0.05	0.00	0.002	0.05
0.36988	2	2	4	100	100	400	0.55	0.62	0.6	-0.05	0.02	0.002	0.05
0.58359	4	4	8	100	100	800	0.55	0.62	0.6	-0.05	0.02	0.002	0.05
0.73497	6	6	12	100	100	1200	0.55	0.62	0.6	-0.05	0.02	0.002	0.05
0.83629	8	8	16	100	100	1600	0.55	0.62	0.6	-0.05	0.02	0.002	0.05
0.90129	10	10	20	100	100	2000	0.55	0.62	0.6	-0.05	0.02	0.002	0.05
0.52013	2	2	4	100	100	400	0.55	0.64	0.6	-0.05	0.04	0.002	0.05
0.77421	4	4	8	100	100	800	0.55	0.64	0.6	-0.05	0.04	0.002	0.05
0.90176	6	6	12	100	100	1200	0.55	0.64	0.6	-0.05	0.04	0.002	0.05
0.95959	8	8	16	100	100	1600	0.55	0.64	0.6	-0.05	0.04	0.002	0.05
0.98407	10	10	20	100	100	2000	0.55	0.64	0.6	-0.05	0.04	0.002	0.05
0.66945	2	2	4	100	100	400	0.55	0.66	0.6	-0.05	0.06	0.002	0.05
0.90359	4	4	8	100	100	800	0.55	0.66	0.6	-0.05	0.06	0.002	0.05
0.97530	6	6	12	100	100	1200	0.55	0.66	0.6	-0.05	0.06	0.002	0.05
0.99420	8	8	16	100	100	1600	0.55	0.66	0.6	-0.05	0.06	0.002	0.05
0.99872	10	10	20	100	100	2000	0.55	0.66	0.6	-0.05	0.06	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 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.
D0 The non-inferiority difference. This is the largest difference between P1 and P2 for which group 1 will be considered non-inferior to group 2.
D1 The actual proportion difference at which the power is calculated. D1 = 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

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 margin of -0.05 (H0: P1 - P2 ≤ -0.05 versus H1: P1 - P2 > -0.05). The comparison will be made using a one-sided Likelihood Score Test (Farrington & Manning) based on the proportion difference (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 difference (P1 - P2) of 0 (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 0.23867.

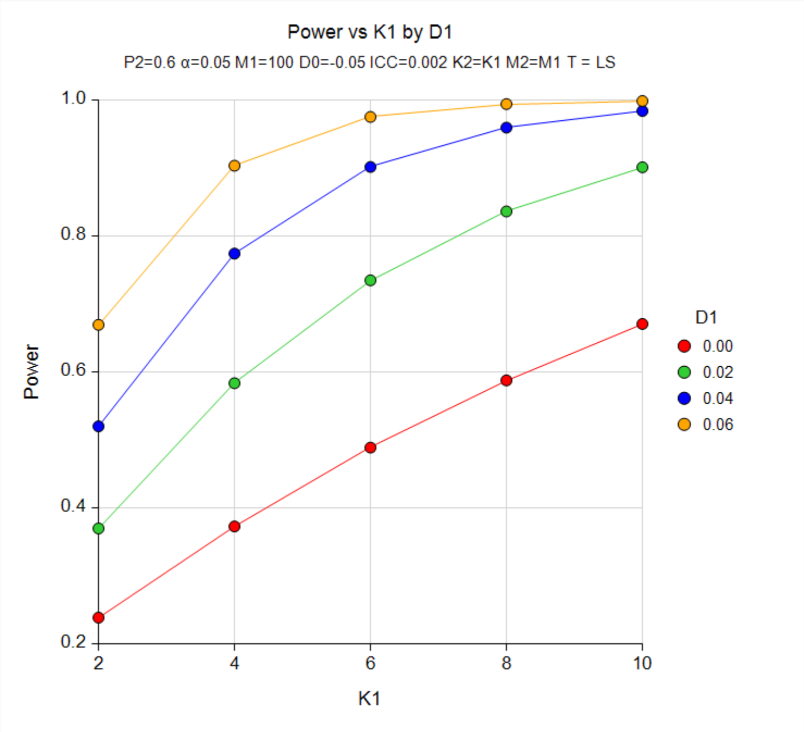
References

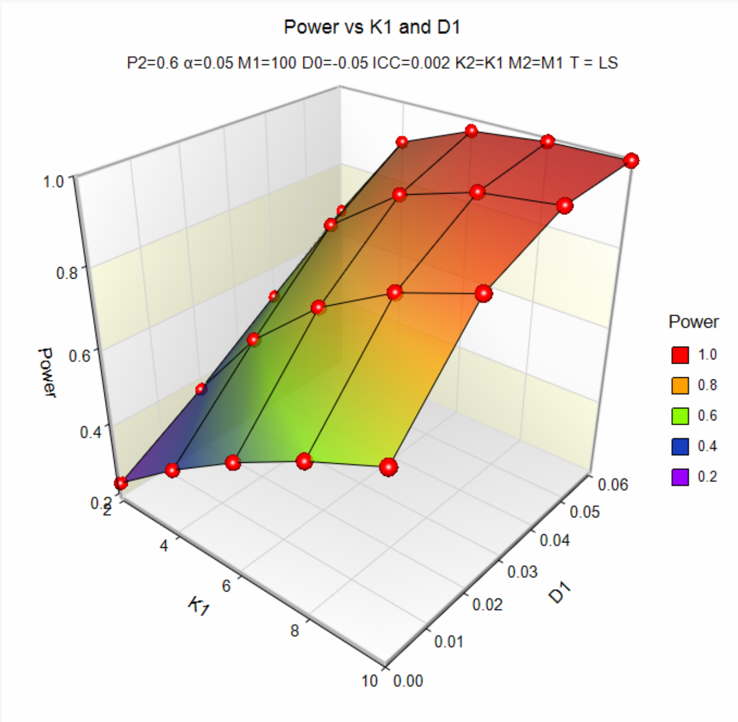
Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.
Chow, S.C. and Liu, J.P. 1999. Design and Analysis of Bioavailability and Bioequivalence Studies. Marcel Dekker. New York.
Donner, A. and Klar, N. 2000. Design and Analysis 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.

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





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 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

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 > D0)**
Test Type	**Likelihood Score (Farr. & Mann.)**
Power	**0.80**
Alpha	**0.05**
M1 (Average Cluster Size)	**100**
K2 (Clusters in Group 2)	**K1**
M2 (Average Cluster Size)	**M1**
Input Type	**Differences**
D0 (Non-Inferiority Difference)	**-0.05**
D1 (Actual Difference)	**0 0.02 0.04 0.06**
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 ≤ D0 vs. H1: P1 - P2 > D0

	Number of Clusters			Cluster Size		Total Sample Size	Proportions			Difference		Intracluster Correlation	
Power	K1	K2	K	M1	M2	N	Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority D0	Actual D1	ICC	Alpha
0.81875	15	15	30	100	100	3000	0.55	0.60	0.6	-0.05	0.00	0.002	0.05
0.83629	8	8	16	100	100	1600	0.55	0.62	0.6	-0.05	0.02	0.002	0.05
0.84985	5	5	10	100	100	1000	0.55	0.64	0.6	-0.05	0.04	0.002	0.05
0.81783	3	3	6	100	100	600	0.55	0.66	0.6	-0.05	0.06	0.002	0.05

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, less expensive treatment works at least as well as the current treatment. They believe, in fact, that the new treatment is about 0.10 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 no less than 0.05 in proportion of success below the current treatment to be considered non-inferior. The proportion of patients responding to the current treatment was 821/1000 = 0.821. The proportion of patients responding to the new treatment was 819/1000 = 0.819. This result did not show significant non-inferiority at the 0.05 level. The researchers want to know the power of their non-inferiority test. They decide to use the intracluster correlation coefficient estimated from the data, which was 0.0068. Although the observed difference in proportions is 0.819 – 0.821 = -0.002, the trivial difference is still -0.05. This value is used in the power calculation.

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	**Power**
Higher Proportions Are	**Better (H1: P1 - P2 > D0)**
Test Type	**Likelihood Score (Farr. & Mann.)**
Alpha	**0.05**
K1 (Clusters in Group 1)	**10**
M1 (Average Cluster Size)	**100**
K2 (Clusters in Group 2)	**K1**
M2 (Average Cluster Size)	**M1**
Input Type	**Differences**
D0 (Non-Inferiority Difference)	**-0.05**
D1 (Actual Difference)	**0.0 0.10**
P2 (Group 2 Proportion)	**0.821**
ICC (Intracluster Correlation)	**0.0068**

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: H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 > D0

	Number of Clusters			Cluster Size		Total Sample Size	Proportions			Difference		Intracluster Correlation	
Power	K1	K2	K	M1	M2	N	Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority D0	Actual D1	ICC	Alpha
0.72698	10	10	20	100	100	2000	0.771	0.821	0.821	-0.05	0.0	0.0068	0.05
1.00000	10	10	20	100	100	2000	0.771	0.921	0.821	-0.05	0.1	0.0068	0.05

If indeed the new treatment were 0.10 higher in proportion of success, the power for showing non-inferiority would be 1.0000. If the true proportions are the same, the power would be 0.72698.

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.