

Chapter 186

Non-Inferiority Tests for Two Proportions in a Cluster-Randomized Design with Clustering in Only One Arm

Introduction

This module provides power analysis and sample size calculation for non-inferiority tests of the difference between two groups when one group has clusters of subjects while the other group is composed completely of individually randomized subjects (no clusters). The outcome is binary.

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are put into a treatment group or a control group. In this case, the proportions of the two arms (groups), where the first is made up of K_i clusters of M_{ij} individuals each and the second arm is made up of individuals (no clusters), are to be tested using a modified z test.

For example, one arm might receive individual intervention (such as medicine) while the other receives this medicine plus some type of group therapy session. The fact that they attend this therapy session implies that they are “clustered”. Thus the clustering occurs in only one arm.

Technical Details

Our formulation comes from Donner and Klar (2000) and Moerbeek and Wong (2008). The latter combine two mixed models: one arm is made up of clusters of subjects while the other arm is made up of individuals. Let y_i be a binary variable that is one of a certain outcome is observed and zero otherwise. The treatment effect is measured by $D = P_1 - P_2$. This can be estimated by

$$\hat{D} = \bar{y}_1 - \bar{y}_2 - D0$$

where \bar{y}_1 and \bar{y}_2 are the estimators of the probabilities of the outcome $y_i = 1$, P_1 and P_2 . $D0$ is called the non-inferiority margin or the non-inferiority difference.

The treatment effect may be tested for statistical significance using

$$\hat{D} / \sqrt{\text{var}(\hat{D})}$$

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The variance of this estimator is

$$\text{var}(\hat{D}) = P_2(1 - P_2) \left(\tau \frac{(\bar{m} - 1)\rho + 1}{\bar{m}k} + \frac{1}{N_2} \right)$$

where \bar{m} is the average cluster size, N_2 is the number of subjects in the non-clustered arm, ρ is intraclass correlation coefficient, and τ is the ratio of the variances of the outcome when $\rho = 0$,

$$\tau = \frac{P_1(1 - P_1)}{P_2(1 - P_2)}.$$

Assume that $D = P_1 - P_2$ is to be tested using a z-test. The statistical hypotheses are $H_0: D \leq D0$ vs. $H_1: D > D0$. The test statistic

$$z = \frac{\bar{Y}_1 - \bar{Y}_2 - D0}{\sqrt{\text{var}(\hat{D})}}$$

has an approximate normal distribution for a *subject-level* analysis.

Using the above, a large sample formula for computing the power of a one-sided test of the significance of the treatment effect at significance level α can be derived from

$$\text{var}(\hat{D}) = \left(\frac{D - D0}{z_{1-\alpha} + z_{\text{power}}} \right)^2$$

Example 1 – Calculating Sample Size

Suppose that a cluster randomized study is to be conducted in which one arm (group 2) will receive an individual medical intervention while the other arm (group 1) receives this medicine plus a special group therapy session conducted by a trained therapist. These therapy sessions will be treated as clusters. Here, group 2 (the non-clustered subjects) are called the *control* group and group 1 (the clustered subjects) are called the *treatment* group. The researchers want to show that the treatment group is non-inferior to the control group by no more than a trivial amount which they set at -0.15. The researchers want to explore what happens as the actual difference is varied between -0.02 and 0.02.

The parameter values are set as follows: $\alpha = 0.025$, $power = 0.9$, $D0 = -0.15$, $D1 = -0.02, 0.0, 0.02$, $PC = 0.4$, $\rho = 0.036$, and $M1 = 10$.

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
Assign Group 1 (Clusters) to be the.....	Treatment Group
Higher Proportions Are	Better (H1: PT - PC > D0 D0 < 0)
Power.....	0.90
Alpha.....	0.025
Group Allocation	Equal, solve for K1 and N2
M1 (Average Cluster Size).....	10
Input Type.....	Differences
D0 (Non-Inferiority Difference)	-0.15
D1 (Actual Difference).....	-0.02 0.0 0.02
PC (Control Group Proportion)	0.4
ρ (Intracluster Correlation, ICC).....	0.036

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
 Group 1 Assignment: Group 1 has Clusters and is the Treatment Group
 Group 2 Assignment: Group 2 does not have Clusters and is the Control Group
 Group Allocation: Equal, solve for K1 and N2
 Higher Proportion are: Better
 Hypotheses: H0: $D1 \leq D0$ vs. H1: $D1 > D0$

Power	Group 1 (Treatment) Clusters		Sample Size (Subjects)			Proportion			Difference			ICC ρ	Alpha
	Number of Clusters K1	Average Cluster Size M1	Group 1 Treatment N1	Group 2 Control N2	Total N	Non-Inferiority PT.0	Actual PT.1	Control PC	Non-Inferiority D0	Actual D1			
0.90553	35	10	350	350	700	0.25	0.38	0.4	-0.15	-0.02	0.036	0.025	
0.90993	27	10	270	270	540	0.25	0.40	0.4	-0.15	0.00	0.036	0.025	
0.90736	21	10	210	210	420	0.25	0.42	0.4	-0.15	0.02	0.036	0.025	

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 K1 The number of clusters in group 1.
 M1 The average cluster size (number of subjects) of the clusters in group 1.
 N1, N2, and N The number of subjects in groups 1 and 2, and their total. Note that $N1 = K1 \times M1$.
 PT.0 The value of the response proportion of group T (Treatment) assumed by the null hypothesis, H0. This is the non-inferiority proportion.
 PT.1 The value of the response proportion of group T (Treatment) assumed by the alternative hypothesis, H1.
 PC The value of the response proportion of group C (Control) assumed by both H0 and H1.
 D0 The value of the difference in response proportions (PT.0 - PC) assumed by the null hypothesis, H0. This is the non-inferiority difference.
 D1 The value of the difference in response proportions (PT.1 - PC) assumed by the alternative hypothesis, H1. This is the difference at which the power is calculated.
 ρ The intraclass correlation (ICC). The correlation between a pair of subjects within a cluster.
 Alpha The probability of rejecting a true null hypothesis.

Summary Statements

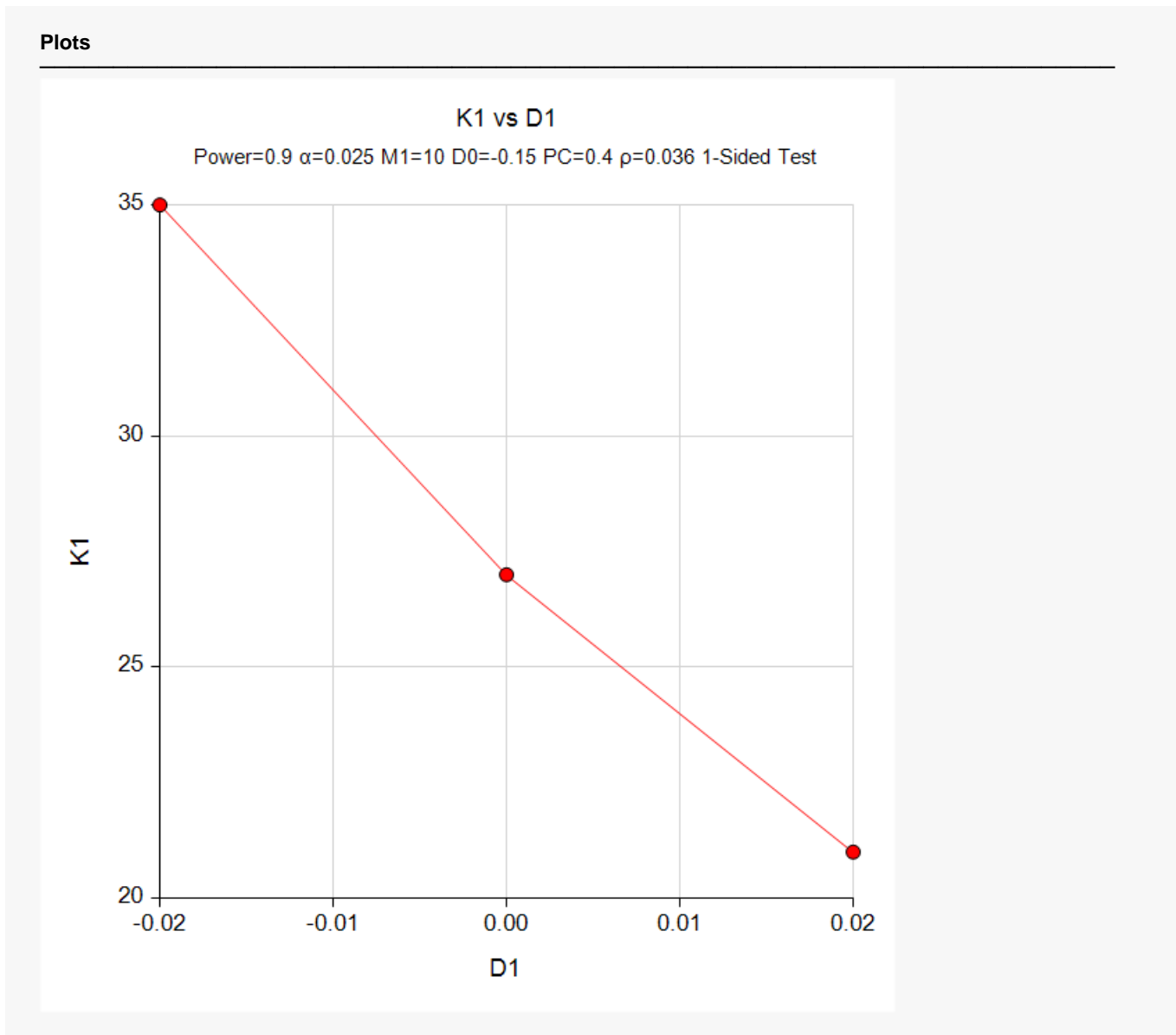
A parallel, two-group design (where higher proportions are considered to be better), with cluster-randomized subjects in Group 1 only (the treatment group), and no clustering in Group 2 (the control group), will be used to test whether the treatment proportion (PT) of Group 1 is non-inferior to the control proportion (PC) of Group 2, with a non-inferiority margin of -0.15 (H0: $D \leq -0.15$ versus H1: $D > -0.15$, $D = PT - PC$). The comparison will be made using a one-sided mixed model Z-test with a Type I error rate (α) of 0.025. The intraclass correlation coefficient for Group 1 (the treatment group) is assumed to be 0.036. To detect a difference (PT - PC) of -0.02 (PT = 0.38 and PC = 0.4), with 10 subjects per cluster in the treatment group (Group 1) and 350 subjects in the control group (Group 2), with 90% power, the number of needed clusters in the treatment group (Group 1) is 35 (totaling 350 subjects in the treatment group).

References

Moerbeek, M. and Wong, W.K. 2008. 'Sample size formulae for trials comparing group and individual treatments in a multilevel model.' *Statistics in Medicine*, Vol. 27, pages 2850-2864.
 Donner, A. and Klar, N. 2000. *Design and Analysis of Cluster Randomization Trials in Health Research*. Arnold. London.

This report shows the power for each of the scenarios.

Plots Section



This plot shows the number of clusters versus D1.

Example 2 – Validation using a Previously Validated PASS Procedure

We could not find a validation example in the literature, so we will validate this procedure by comparing its results with that of a previously validated procedure, **Non-Inferiority Tests for the Difference of Two Proportions in a Cluster-Randomized Design**, which calculates power for an identical problem when the cluster size in the second group is set to 1. We will use the first row from Example 1 as the parameter settings for this procedure. The resulting power should be 0.90553.

Setup of the Validation Procedure

If the **Non-Inferiority Tests for the Difference of Two Proportions in a Cluster-Randomized Design** 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 **Validation of Only One Clustered Arm Procedure** 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.....	Z-Test (Unpooled)
Alpha.....	0.025
K1 (Clusters in Group 1)	35
M1 (Average Cluster Size).....	10
K2 (Clusters in Group 2)	350
M2 (Average Cluster Size).....	1
Input Type.....	Differences
D0 (Non-Inferiority Difference)	-0.15
D1 (Actual Difference).....	-0.02
P2 (Group 2 Proportion).....	0.4
ICC (Intracluster Correlation).....	0.036

Validation 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: Z-Test (Unpooled)													
Hypotheses: H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 > D0													
Power	Number of Clusters			Cluster Size		Total Sample Size N	Proportions			Difference		Intracluster Correlation ICC	Alpha
	K1	K2	K	M1	M2		Non-Inferiority P1.0	Actual P1.1	Reference P2	Non-Inferiority D0	Actual D1		
0.90553	35	350	385	10	1	700	0.25	0.38	0.4	-0.15	-0.02	0.036	0.025

PASS calculates a power of 0.90553 which matches the first line result from Example 1.

Setup

We will now present the example in the current procedure. In this case, we will enter the sample size values and calculate the power.

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
Assign Group 1 (Clusters) to be the.....	Treatment Group
Higher Proportions Are	Better (H1: PT - PC > D0 D0 < 0)
Alpha.....	0.025
Group Allocation	Enter K1 and N2 individually
K1 (Number of Clusters)	35
M1 (Average Cluster Size).....	10
N2 (Number of Subjects)	350
Input Type.....	Differences
D0 (Non-Inferiority Difference)	-0.15
D1 (Actual Difference).....	-0.02
PC (Control Group Proportion)	0.4
ρ (Intracluster Correlation, ICC).....	0.036

Output

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

Numeric Results

Solve For: [Power](#)
 Group 1 Assignment: Group 1 has Clusters and is the Treatment Group
 Group 2 Assignment: Group 2 does not have Clusters and is the Control Group
 Group Allocation: Enter K1 and N2 individually
 Higher Proportion are: Better
 Hypotheses: $H_0: D_1 \leq D_0$ vs. $H_1: D_1 > D_0$

	Group 1 (Treatment) Clusters		Sample Size (Subjects)			Proportion			Difference			ICC	
	Number of Clusters K1	Average Cluster Size M1	Group 1 Treatment N1	Group 2 Control N2	Total N	Non-Inferiority PT.0	Actual PT.1	Control PC	Non-Inferiority D0	Actual D1	ρ	Alpha	
Power													
0.90553	35	10	350	350	700	0.25	0.38	0.4	-0.15	-0.02	0.036	0.025	

PASS calculates a power of 0.90553 which matches the first line result from Example 1 and the other procedure.