

Chapter 167

Multi-Arm Non-Inferiority Tests for the Odds Ratio of Treatment and Control Proportions

Introduction

This module computes power and sample size for multi-arm, noninferiority tests of the odds ratio of treatment and control proportions. This procedure is based on the results in Machin, Campbell, Tan, and Tan (2018). In this design, there are k treatment groups and one control group. The groups are independent and are sampled using simple random sampling. A proportion is measured in each group. A total of k hypothesis tests are anticipated each comparing a treatment group with the common control group using a noninferiority test of the odds ratio of two proportions.

The Bonferroni multiplicity adjustment of the type I error rate may be optionally made because several tests are being constructed from 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.

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 popular three-arm design consists of three groups: control, treatment A, and treatment B. Two tests are run: treatment A versus control and treatment B versus the same control. This avoids having to obtain a second control group for treatment B. Besides the obvious efficiency in subjects, it may be easier to recruit subjects if their chances of receiving a new treatment are better than 50%.

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. Hence, three groups are needed to complete this study. Two non-inferiority hypotheses need to be tested in this study: whether each new treatment is as good as the current treatment.

Because of the many benefits of the new treatment, clinicians are willing to adopt a new treatment even if it is slightly less effective than the current treatment. They must determine, however, how much less effective the new treatment can be and still be adopted. Should it be adopted if its odds ratio with the control group is 0.95? 0.925? 0.9? 0.8? There is an odds ratio that is so low that decrease in response is no longer ignorable. In this example, after thoughtful discussion with several clinicians, it was decided that if a response odds ratio of at least 0.80 is achieved, the new treatment will be adopted. The odds ratio between these two percentages is called the *non-inferiority odds ratio* (OR_0).

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The developers must design an experiment to test the hypothesis that the response odds ratio is at least 0.8. The statistical hypotheses to be tested are

$$H_0: OR_A \leq OR_0 \quad \text{vs.} \quad H_1: OR_A > OR_0$$

$$H_0: OR_B \leq OR_0 \quad \text{vs.} \quad H_1: OR_B > OR_0$$

where $OR_0 = 0.8$.

Notice that when the null hypothesis is rejected, the conclusion is that the odds ratio is at least 0.8.

Technical Details

The details of sample size calculation for the two-sample design for binary outcomes are presented in the chapter "Tests for Two Proportions," and they will not be duplicated here. Instead, this chapter only discusses those changes necessary for non-inferiority tests.

Suppose you have k treatment groups with response probabilities P_i of size N_i and one control group with response probability P_C of size N_C . The total sample size is $N = N_1 + N_2 + \dots + N_k + N_C$.

Let $O_i = p_i/(1 - p_i)$ represent the *odds* for group i . The k one-sided noninferiority tests are

$$H_{0i}: O_i/O_C \leq OR_0 \quad \text{vs.} \quad H_{1i}: O_i/O_C > OR_0 \quad \text{for } i = 1, 2, \dots, k.$$

Note that for noninferiority tests, if higher proportions are better, $OR_0 < 1$ and if lower proportions are better, $OR_0 > 1$.

If we define $OR_i = O_i/O_C$, these are equivalent to

$$H_{0i}: OR_i \leq OR_0 \quad \text{vs.} \quad H_{1i}: OR_i > OR_0 \quad \text{for } i = 1, 2, \dots, k$$

For convenience, these hypotheses are collectively referred to as

$$H_0: OR \leq OR_0 \quad \text{vs.} \quad H_1: OR > OR_0$$

Test Statistics

Two test statistics are available in this procedure. These tests are both likelihood score tests.

Miettinen and Nurminen's Likelihood Score Test

Miettinen and Nurminen (1985) proposed a test statistic for testing whether the odds ratio is equal to a specified value, OR_0 . Because the approach they used with the difference and ratio does not easily extend to the odds ratio, they used a score statistic approach for the odds ratio. The regular MLE's are \hat{p}_1 and \hat{p}_2 . The constrained MLE's are \tilde{p}_1 and \tilde{p}_2 . These estimates are constrained so that $\tilde{OR} = OR_0$. A correction factor of $N/(N-1)$ is applied to make the variance estimate less biased. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

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The formula for computing the test statistic is

$$z_{MNO} = \frac{\frac{(\hat{p}_i - \tilde{p}_i)}{\tilde{p}_i \tilde{q}_i} - \frac{(\hat{p}_c - \tilde{p}_c)}{\tilde{p}_c \tilde{q}_c}}{\sqrt{\left(\frac{1}{n_i \tilde{p}_i \tilde{q}_i} + \frac{1}{n_c \tilde{p}_c \tilde{q}_c}\right) \left(\frac{N}{N-1}\right)}}$$

where

$$\tilde{p}_i = \frac{\tilde{p}_c OR_0}{1 + \tilde{p}_c (OR_0 - 1)}$$

$$\tilde{p}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

$$A = n_c (OR_0 - 1),$$

$$B = n_i OR_0 + n_c - m_1 (OR_0 - 1),$$

$$C = -m_1$$

$$m_1 = \text{number of successes}$$

Farrington and Manning's Likelihood Score Test

Farrington and Manning (1990) indicate that the Miettinen and Nurminen statistic may be modified by removing the factor $N/(N-1)$.

The formula for computing this test statistic is

$$z_{FMO} = \frac{\frac{(\hat{p}_i - \tilde{p}_i)}{\tilde{p}_i \tilde{q}_i} - \frac{(\hat{p}_c - \tilde{p}_c)}{\tilde{p}_c \tilde{q}_c}}{\sqrt{\left(\frac{1}{n_i \tilde{p}_i \tilde{q}_i} + \frac{1}{n_c \tilde{p}_c \tilde{q}_c}\right)}}$$

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

Asymptotic Approximation to Power

A large sample approximation is used to compute power. The large sample approximation is made by replacing the values of \hat{p}_i and \hat{p}_c in the z statistic with the corresponding values of p_i and p_c , and then computing the results based on the normal distribution.

Multiplicity Adjustment

Because k tests between treatment groups and the control group are run when analyzing the results of this study, many statisticians recommend that the 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 will be conducted using an alpha of 0.01.

The main criticism of this procedure is that if there are many tests, 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 by 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 subjects in this group. The standard adjustment is to include \sqrt{k} subjects in the control group for each subject 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 size.

Example 1 – Finding the Sample Size

A parallel-group, clinical trial is being designed to compare three doses of a test compound against the standard therapy using three non-inferiority Farrington and Manning Likelihood Scores tests. Suppose the standard therapy has a response rate of 0.6. The investigators would like a sample size large enough to find statistical significance at an overall 0.05 level and an individual-test power of 0.90. The response rates of treatment group 1 are 0.62, 0.65, 0.68. The response rate of group 2 is 0.7. The response rate of group 3 is 0.75. The non-inferiority odds ratio is 0.8.

Following common practice, the control-group sample-size multiplier will be set to $\sqrt{k} = \sqrt{3} = 1.732$ since there are three treatment groups in this design.

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
Higher Proportions Are	Better (H1: OR > OR0)
Test Type.....	Likelihood Score (Farr. & Mann.)
Power of Each Test	0.90
Overall Alpha	0.05
Bonferroni Adjustment	Standard Bonferroni
Group Allocation	Enter Group Allocation Pattern, solve for group sample sizes
OR0 (Non-Inferiority Odds Ratio).....	0.8
Control Proportion.....	0.6
Control Sample Size Allocation.....	1
Set A Number of Groups.....	1
Set A Proportion	0.62 0.65 0.68
Set A Sample Size Allocation	1
Set B Number of Groups.....	1
Set B Proportion	0.7
Set B Sample Size Allocation	1
Set C Number of Groups	1
Set C Proportion	0.75
Set C Sample Size Allocation	1
Set D Number of Groups	0
More.....	Unchecked

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 sample sizes
 Test Type: Farrington & Manning Likelihood Score Test
 Higher Proportions Are: Better
 Hypotheses: H0: OR ≤ OR0 vs. H1: OR > OR0
 Number of Groups: 4
 Bonferroni Adjustment: Standard Bonferroni (Divisor = 3)

Comparison	Power		Sample Size		Proportion		Odds Ratio		Alpha	
	Target	Actual	Ni	Allocation	Pi H0 Pi.0	Pi H1 Pi.1	NI OR0	Actual ORi	Overall	Bonferroni- Adjusted
Control			1033	1	0.60000	0.60				
vs A	0.9	0.90016	1033	1	0.54545	0.62	0.8	1.08772	0.05	0.016667
vs B	0.9	1.00000	1033	1	0.54545	0.70	0.8	1.55556	0.05	0.016667
vs C	0.9	1.00000	1033	1	0.54545	0.75	0.8	2.00000	0.05	0.016667
Total			4132							
Control			520	1	0.60000	0.60				
vs A	0.9	0.90035	520	1	0.54545	0.65	0.8	1.23810	0.05	0.016667
vs B	0.9	0.99846	520	1	0.54545	0.70	0.8	1.55556	0.05	0.016667
vs C	0.9	1.00000	520	1	0.54545	0.75	0.8	2.00000	0.05	0.016667
Total			2080							
Control			310	1	0.60000	0.60				
vs A	0.9	0.90003	310	1	0.54545	0.68	0.8	1.41667	0.05	0.016667
vs B	0.9	0.96429	310	1	0.54545	0.70	0.8	1.55556	0.05	0.016667
vs C	0.9	0.99907	310	1	0.54545	0.75	0.8	2.00000	0.05	0.016667
Total			1240							

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 odds ratio.

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.

Ni: Sample Size. The number of subjects in the ith group. The total sample size, N, is shown as the last row of the column.

Allocation: The group sample size allocation pattern. The value on each row represents the relative number of subjects assigned to the group.

Pi.0: The response proportion in the ith group assumed by the null hypothesis, H0. Note that Pi.0 = f(Pc, OR0), where Pc is the control group proportion.

Pi.1: The response proportion in the ith group at which the power is calculated.

OR0: The non-inferiority odds ratio boundary used to declare whether the treatment is non-inferior or not.

ORi: The odds ratio of the ith treatment group proportion (Pi.1) and the control group proportion (Pc) at which the power is calculated.

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, 4-group design (with one control group and 3 treatment groups) will be used to test whether the proportion for each treatment group is non-inferior to the control group proportion, with a non-inferiority odds ratio of 0.8 (H0: OR ≤ 0.8 vs. H1: OR > 0.8, OR = [Pi / (1 - Pi)] / [Pc / (1 - Pc)]). In this study, higher proportions are considered to be better. The non-inferiority hypotheses will be evaluated using 3 one-sided, two-sample, Bonferroni-adjusted Farrington & Manning Likelihood Score tests of the odds ratio, with an overall (experiment-wise) Type I error rate (α) of 0.05. The control group proportion is assumed to be 0.6. To detect the treatment proportions 0.62, 0.7, and 0.75 with at least 90% power for each test, the control group sample size needed will be 1033 and the number of needed subjects for the treatment groups will be 1033, 1033, and 1033 (totaling 4132 subjects overall).

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Dropout-Inflated Sample Size

Group	Dropout Rate	Sample Size Ni	Dropout- Inflated Enrollment Sample Size Ni'	Expected Number of Dropouts Di
1 - 4	20%	1033	1292	259
Total		4132	5168	1036
1 - 4	20%	520	650	130
Total		2080	2600	520
1 - 4	20%	310	388	78
Total		1240	1552	312

Group	Lists the group numbers.
Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
Ni	The evaluable sample size for each group at which power is computed (as entered by the user). If Ni subjects are evaluated out of the Ni' subjects that are enrolled in the study, the design will achieve the stated power.
Ni'	The number of subjects that should be enrolled in each group in order to obtain Ni evaluable subjects, based on the assumed dropout rate. Ni' is calculated by inflating Ni using the formula $Ni' = Ni / (1 - DR)$, with Ni' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. (2018) pages 32-33.)
Di	The expected number of dropouts in each group. $Di = Ni' - Ni$.

Dropout Summary Statements

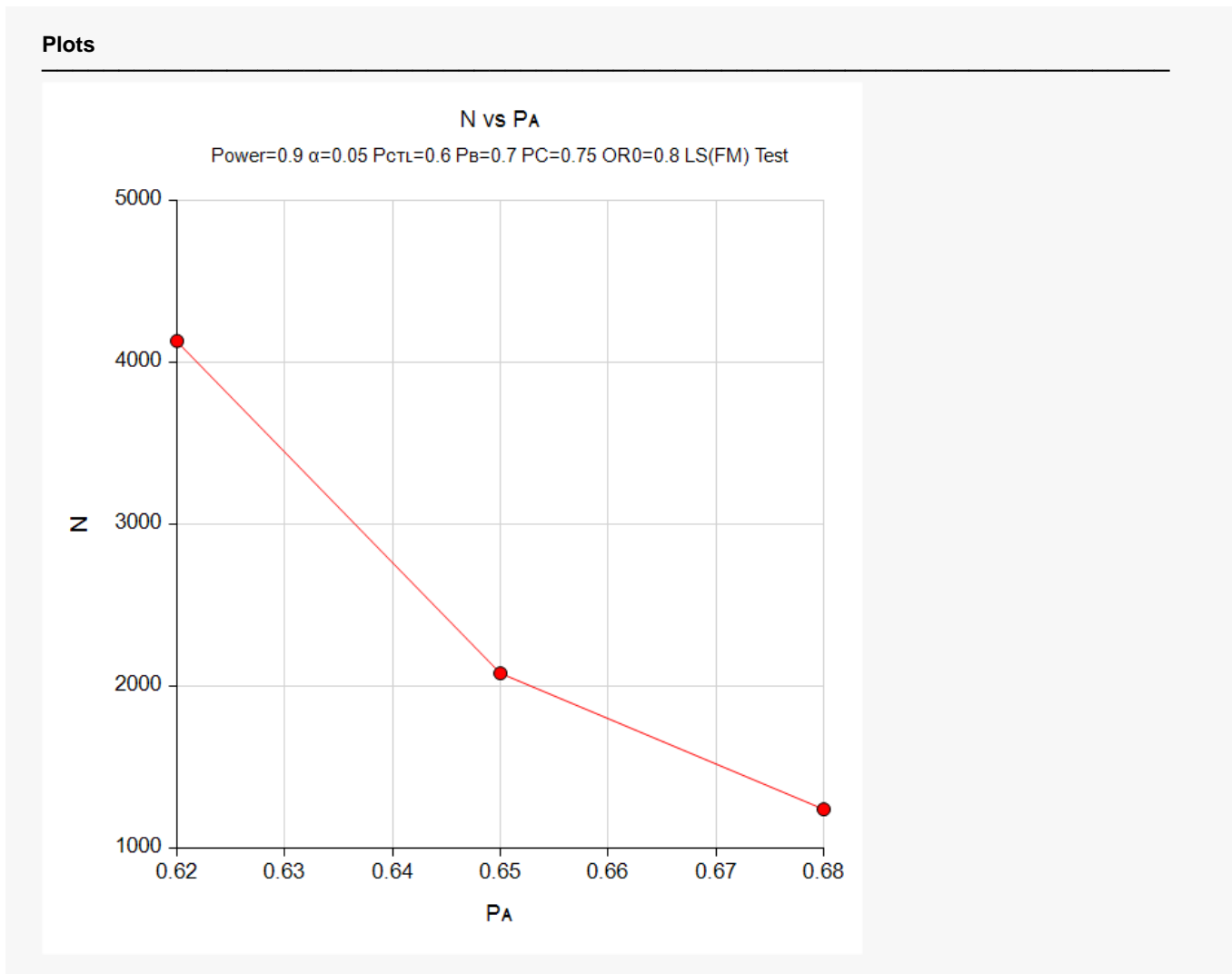
Anticipating a 20% dropout rate, group sizes of 1292, 1292, 1292, and 1292 subjects should be enrolled to obtain final group sample sizes of 1033, 1033, 1033, and 1033 subjects.

References

- Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. 2018. Sample Size Calculations in Clinical Research, 3rd Edition. Chapman & Hall/CRC. Boca Raton, FL. Pages 86-88.
- D'Agostino, R.B., Chase, W., and Belanger, A. 1988. 'The Appropriateness of Some Common Procedures for Testing the Equality of Two Independent Binomial Populations', The American Statistician, August 1988, Volume 42 Number 3, pages 198-202.
- 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.
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- 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.
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- 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.
- Miettinen, O.S. and Nurminen, M. 1985. 'Comparative analysis of two rates.' Statistics in Medicine 4: 213-226.

This report shows the numeric results of this power study. Notice that the results are shown in blocks of three rows at a time. Each block represents a single design.

Plots Section



This plot gives a visual presentation to the results in the Numeric Report. We can quickly see the impact on the sample size of decreasing the difference between the treatment and control proportions.

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 (**Non-Inferiority Tests for the Odds Ratio of Two Proportions**) to produce the results for the following example.

Suppose a parallel-group, clinical trial is being designed to compare two doses of a test compound against the standard therapy using two noninferiority Miettinen and Nurminen Likelihood Scores tests. Suppose the standard therapy has a response rate of 0.60. The investigators would like a sample size large enough to find statistical significance at an overall 0.05 level and an individual-test power of 0.80. The response rates of groups 1 and 2 are 0.60 and 0.65, respectively. Note that 0.6 and 0.65 correspond to odds ratios of 1.0 and 1.23809524, respectively. The non-inferiority odds ratio is 0.8.

The **Non-Inferiority Tests for the Odds Ratio of Two Proportions** procedure is set up as follows.

Design Tab	
Solve For	Sample Size
Power Calculation Method	Normal Approximation
Higher Proportions Are	Better (H1: OR > OR0)
Test Type.....	Likelihood Score (Miet. & Nurm.)
Power.....	0.8
Alpha.....	0.025 (which is Alpha / k)
Group Allocation	Equal (N1 = N2)
OR0 (Non-Inferiority Odds Ratio).....	0.8
OR1 (Actual Odds Ratio).....	1 1.23809524
P2 (Group 2 Proportion).....	0.6

This set of options generates the following report.

Numeric Results										
Solve For:		Sample Size								
Test Statistic:		Miettinen & Nurminen Likelihood Score Test								
Hypotheses:		H0: OR ≤ OR0 vs. H1: OR > OR0								
Target Power	Actual Power*	N1	N2	N	Ref. P2	P1 H0 P1.0	P1 H1 P1.1	NI OR OR0	OR OR1	Alpha
0.8	0.80029	1312	1312	2624	0.6	0.54545455	0.60	0.8	1.00000000	0.025
0.8	0.80109	352	352	704	0.6	0.54545455	0.65	0.8	1.23809524	0.025

* Power was computed using the normal approximation method.

In order to maintain a power of 80% for both groups, it is apparent that the groups will all need to have a sample size of 1312. We next calculate the powers of the two groups using these sample sizes. The results are displayed in the following table.

Multi-Arm Non-Inferiority Tests for the Odds Ratio of Treatment and Control Proportions

Numeric Results

Solve For: **Power**
 Test Statistic: Miettinen & Nurminen Likelihood Score Test
 Hypotheses: $H_0: OR \leq OR_0$ vs. $H_1: OR > OR_0$

Power*	N1	N2	N	Ref. P2	P1 H0 P1.0	P1 H1 P1.1	NI OR OR0	OR OR1	Alpha
0.80029	1312	1312	2624	0.6	0.54545455	0.60	0.8	1.00000000	0.025
0.99973	1312	1312	2624	0.6	0.54545455	0.65	0.8	1.23809524	0.025

* Power was computed using the normal approximation method.

This table contains the validation values. We will now run these values through the current procedure and compare the results with these values.

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**
 Higher Proportions Are **Better (H1: OR > OR0)**
 Test Type..... **Likelihood Score (Miet. & Nurm.)**
 Power of Each Test **0.8**
 Overall Alpha **0.05**
 Bonferroni Adjustment **Standard Bonferroni**
 Group Allocation **Equal (Nc = N1 = N2 = ...)**
 OR0 (Non-Inferiority Odds Ratio)..... **0.8**
 Control Proportion..... **0.6**
 Set A Number of Groups..... **1**
 Set A Proportion **0.6**
 Set B Number of Groups..... **1**
 Set B Proportion **0.65**
 Set C Number of Groups **0**
 Set D Number of Groups **0**
 More..... **Unchecked**

Multi-Arm Non-Inferiority Tests for the Odds Ratio of Treatment and Control Proportions

Output

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

Numeric Results

Solve For: [Sample Size](#)
 Group Allocation: Equal ($N_c = N_1 = N_2 = \dots$)
 Test Type: Miettinen & Nurminen Likelihood Score Test
 Higher Proportions Are: Better
 Hypotheses: $H_0: OR \leq OR_0$ vs. $H_1: OR > OR_0$
 Number of Groups: 3
 Bonferroni Adjustment: Standard Bonferroni (Divisor = 2)

Comparison	Power		Sample Size N_i	Proportion		Odds Ratio		Alpha	
	Target	Actual		$P_{i H_0}$ $P_{i.0}$	$P_{i H_1}$ $P_{i.1}$	NI OR_0	Actual OR_i	Overall	Bonferroni-Adjusted
Control			1312	0.60000	0.60				
vs A	0.8	0.80029	1312	0.54545	0.60	0.8	1.0000	0.05	0.025
vs B	0.8	0.99973	1312	0.54545	0.65	0.8	1.2381	0.05	0.025
Total			3936						

The sample sizes and powers match which validates this procedure.