

Chapter 227

Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

This procedure uses simulation for the calculation of the boundaries as well as for calculation of power (and sample size). Futility boundaries are limited. A variety of test statistics are available.

Introduction

This procedure can be used to determine power, sample size and/or boundaries for group sequential non-inferiority tests comparing the ratio of proportions from two groups. The tests that can be simulated in this procedure are the common two-sample Z-test with or without pooled standard error and with or without continuity correction, the T-test, and three score tests. Significance and futility boundaries can be produced. The spacing of the looks can be equal or custom specified. Boundaries can be computed based on popular alpha- and beta-spending functions (O'Brien-Fleming, Pocock, Hwang-Shih-DeCani Gamma family, linear) or custom spending functions. Boundaries can also be input directly to verify alpha- and/or beta-spending properties. Futility boundaries can be binding or non-binding. Maximum and average (expected) sample sizes are reported as well as the alpha and/or beta spent and incremental power at each look. Corresponding P-Value boundaries are given for each boundary statistic. Plots of boundaries are also produced.

Technical Details

This section outlines many of the technical details of the techniques used in this procedure including the simulation summary, the test statistic details, and the use of spending functions.

An excellent text for the background and details of many group-sequential methods is Jennison and Turnbull (2000).

Simulation Procedure

In this procedure, a large number of simulations are used to calculate boundaries and power using the following steps

1. Based on the specified proportions, random samples of size N_1 and N_2 are generated under the null distribution and under the alternative distribution. These are simulated samples as though the final look is reached.
2. For each sample, test statistics for each look are produced. For example, if N_1 and N_2 are 100 and there are 5 equally spaced looks, test statistics are generated from the random samples at $N_1 = N_2 = 20$, $N_1 = N_2 = 40$, $N_1 = N_2 = 60$, $N_1 = N_2 = 80$, and $N_1 = N_2 = 100$ for both null and alternative samples.

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3. To generate the first significance boundary, the null distribution statistics of the first look (e.g., at $N_1 = N_2 = 20$) are ordered and the percent of alpha to be spent at the first look is determined (using either the alpha-spending function or the input value). The statistic for which the percent of statistics above (or below, as the case may be) that value is equal to the percent of alpha to be spent at the first look is the boundary statistic. It is seen here how important a large number of simulations is to the precision of the boundary estimates.
4. All null distribution samples that are outside the first significance boundary at the first look are removed from consideration for the second look. If binding futility boundaries are also being computed, all null distribution samples with statistics that are outside the first futility boundary are also removed from consideration for the second look. If non-binding futility boundaries are being computed, null distribution samples with statistics outside the first futility boundary are not removed.
5. To generate the second significance boundary, the remaining null distribution statistics of the second look (e.g., at $N_1 = N_2 = 40$) are ordered and the percent of alpha to be spent at the second look is determined (again, using either the alpha-spending function or the input value). The percent of alpha to be spent at the second look is multiplied by the total number of simulations to determine the number of the statistic that is to be the second boundary statistic. The statistic for which that number of statistics is above it (or below, as the case may be) is the second boundary statistic. For example, suppose there are initially 1000 simulated samples, with 10 removed at the first look (from, say, alpha spent at Look 1 equal to 0.01), leaving 990 samples considered for the second look. Suppose further that the alpha to be spent at the second look is 0.02. This is multiplied by 1000 to give 20. The 990 still-considered statistics are ordered and the 970th (20 in from 990) statistic is the second boundary.
6. All null distribution samples that are outside the second significance boundary and the second futility boundary, if binding, at the second look are removed from consideration for the third look (e.g., leaving 970 statistics computed at $N_1 = N_2 = 60$ to be considered at the third look). Steps 4 and 5 are repeated until the final look is reached.

Futility boundaries are computed in a similar manner using the desired beta-spending function or custom beta-spending values and the alternative hypothesis simulated statistics at each look. For both binding and non-binding futility boundaries, samples for which alternative hypothesis statistics are outside either the significance or futility boundaries of the previous look are excluded from current and future looks.

Because the final futility and significance boundaries are required to be the same, futility boundaries are computed beginning at a small value of beta (e.g., 0.0001) and incrementing beta by that amount until the futility and significance boundaries meet.

When boundaries are entered directly, this procedure uses the null hypothesis and alternative hypothesis simulations to determine the number of test statistics that are outside the boundaries at each look. The cumulative proportion of alternative hypothesis statistics that are outside the significance boundaries is the overall power of the study.

Small Sample Considerations

When the sample size is small, say 200 or fewer per group, the discrete nature of the number of possible differences in proportions in the sampling distribution comes into play. This has led to a large number of proposed tests for comparing two proportions (or testing the 2 by 2 table of counts). For example, Upton (1982) considers twenty-two alternative tests for comparing two proportions. Sweeping statements about the power of one test over another are impossible to make, because the size of the Type I error depends upon the proportions used. At some proportions, some tests are overly conservative while others are not, while at other proportions the reverse may be true.

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This simulation procedure, however, is based primarily on the ordering of the sample statistics in the simulation. The boundaries are determined by the spending function alphas. Thus, if a test used happens to be conservative in the single-look traditional sense, the boundaries chosen in the simulation results of this procedure will generally remove the conservative nature of the test. This makes comparisons to the one-look case surprising in many cases.

Definitions

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability (or risk) of obtaining the event of interest in population 1 (the treatment group) is p_1 and in population 2 (the control group) is p_2 . The corresponding failure proportions are given by $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$.

The assumption is made that the responses from each group follow a binomial distribution. This means that the event probability, p_i , is the same for all subjects within the group and that the response from one subject is independent of that of any other subject.

Random samples of m and n individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows

Group	Success	Failure	Total
Treatment	a	c	m
Control	b	d	n
Total	s	f	N

The following alternative notation is also used.

Group	Success	Failure	Total
Treatment	x_{11}	x_{12}	n_1
Control	x_{21}	x_{22}	n_2
Total	m_1	m_2	N

The binomial proportions p_1 and p_2 are estimated from these data using the formulae

$$\hat{p}_1 = \frac{a}{m} = \frac{x_{11}}{n_1} \quad \text{and} \quad \hat{p}_2 = \frac{b}{n} = \frac{x_{21}}{n_2}$$

Comparing Two Proportions

Let $p_{1.0}$ represent the group 1 proportion tested by the null hypothesis, H_0 . The power of a test is computed at a specific value of the proportion which we will call $p_{1.1}$. Let δ represent the smallest difference (margin of non-inferiority) between the two proportions that still results in the conclusion that the new treatment is not inferior to the current treatment. For a non-inferiority test, $\delta < 0$. The set of statistical hypotheses that are tested is

$$H_0: p_{1.0} - p_2 \leq \delta \text{ versus } H_1: p_{1.0} - p_2 > \delta$$

which can be rearranged to give

$$H_0: p_{1.0} \leq p_2 + \delta \text{ versus } H_1: p_{1.0} > p_2 + \delta$$

There are multiple methods of specifying the margin of non-inferiority. The most direct is to simply give values for p_2 and $p_{1.0}$. However, it is often more meaningful to give p_2 and then specify $p_{1.0}$ implicitly by specifying the difference, ratio, or odds ratio. Mathematically, assuming higher proportions are better, the definitions of these parameterizations are

Parameter	Computation	Hypotheses
Difference	$\delta = p_{1.0} - p_2$	$H_0: p_{1.0} - p_2 \leq \delta_0$ vs. $H_1: p_{1.0} - p_2 > \delta_0$, $\delta_0 < 0$
Ratio	$\phi = p_{1.0} / p_2$	$H_0: p_1 / p_2 \leq \phi_0$ vs. $H_1: p_1 / p_2 > \phi_0$, $\phi_0 < 1$
Odds Ratio	$\psi = Odds_{1.0} / Odds_2$	$H_0: o_{1.0} / o_2 \leq \psi_0$ vs. $H_1: o_{1.0} / o_2 > \psi_0$, $\psi_0 < 1$

Ratio

The ratio, $\phi = p_{1.0} / p_2$, gives the relative change in the probability of the response. Testing non-inferiority uses the formulation

$$H_0: p_{1.0} / p_2 \leq \phi_0 \text{ versus } H_1: p_{1.0} / p_2 > \phi_0$$

when higher proportions are better.

The following example is used to convey the concept of *non-inferiority* as defined by the ratio. Suppose that 60% of patients ($p_2 = 0.60$) respond to the current treatment method. If a new treatment decreases the response rate by no more than 10% ($\phi_0 = 0.90$), it will be considered non-inferior to the standard treatment. Substituting these figures into the statistical hypotheses gives

$$H_0: \phi \leq 0.90 \text{ versus } H_1: \phi > 0.90$$

Using the relationship

$$p_{1.0} = \phi_0 p_2$$

gives

$$H_0: p_{1.0} \leq 0.54 \text{ versus } H_1: p_{1.0} > 0.54$$

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In this example, when the null hypothesis is rejected, the concluded alternative is that the response rate is at least 54%. That is, the conclusion of non-inferiority is that the new treatment's response rate is no worse than 10% less than that of the standard treatment.

Test Statistics

This section describes the test statistics that are available in this procedure.

Miettinen and Nurminen's Likelihood Score Test

Miettinen and Nurminen (1985) proposed a test statistic for testing whether the ratio is equal to a specified value ϕ_0 . The regular MLE's, \hat{p}_1 and \hat{p}_2 , are used in the numerator of the score statistic while MLE's \tilde{p}_1 and \tilde{p}_2 , constrained so that $\tilde{p}_1 / \tilde{p}_2 = \phi_0$, are used in the denominator. 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.

The formula for computing the test statistic is

$$Z_{MNR} = \frac{\hat{p}_1 / \hat{p}_2 - \phi_0}{\sqrt{\left(\frac{\tilde{p}_1 \tilde{q}_1}{n_1} + \phi_0^2 \frac{\tilde{p}_2 \tilde{q}_2}{n_2}\right) \left(\frac{N}{N-1}\right)}}$$

where

$$\tilde{p}_1 = \tilde{p}_2 \phi_0$$

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

$$A = N\phi_0$$

$$B = -[n_1\phi_0 + x_{11} + n_2 + x_{21}\phi_0]$$

$$C = m_1$$

Farrington and Manning's Likelihood Score Test

Farrington and Manning (1990) proposed a test statistic for testing whether the ratio is equal to a specified value ϕ_0 . The regular MLE's, \hat{p}_1 and \hat{p}_2 , are used in the numerator of the score statistic while MLE's \tilde{p}_1 and \tilde{p}_2 , constrained so that $\tilde{p}_1 / \tilde{p}_2 = \phi_0$, are used in the denominator. A correction factor of $N/(N-1)$ is applied to increase the variance estimate. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{FMR} = \frac{\hat{p}_1 / \hat{p}_2 - \phi_0}{\sqrt{\left(\frac{\tilde{p}_1 \tilde{q}_1}{n_1} + \phi_0^2 \frac{\tilde{p}_2 \tilde{q}_2}{n_2}\right)}}$$

where the estimates \tilde{p}_1 and \tilde{p}_2 are computed as in the corresponding test of Miettinen and Nurminen (1985) given above.

Gart and Nam's Likelihood Score Test

Gart and Nam (1988), page 329, proposed a modification to the Farrington and Manning (1988) ratio test that corrects for skewness. Let $z_{FMR}(\phi)$ stand for the Farrington and Manning ratio test statistic described above. The skewness corrected test statistic, z_{GNR} , is the appropriate solution to the quadratic equation

$$(-\tilde{\varphi})z_{GNR}^2 + (-1)z_{GNR} + (z_{FMR}(\phi) + \tilde{\varphi}) = 0$$

where

$$\tilde{\varphi} = \frac{1}{6\tilde{u}^{3/2}} \left(\frac{\tilde{q}_1(\tilde{q}_1 - \tilde{p}_1)}{n_1^2 \tilde{p}_1^2} - \frac{\tilde{q}_2(\tilde{q}_2 - \tilde{p}_2)}{n_2^2 \tilde{p}_2^2} \right)$$

$$\tilde{u} = \frac{\tilde{q}_1}{n_1 \tilde{p}_1} + \frac{\tilde{q}_2}{n_2 \tilde{p}_2}$$

Spending Functions

Spending functions can be used in this procedure to specify the proportion of alpha or beta that is spent at each look without having to specify the proportion directly.

Spending functions have the characteristics that they are increasing and that

$$\alpha(0) = 0$$

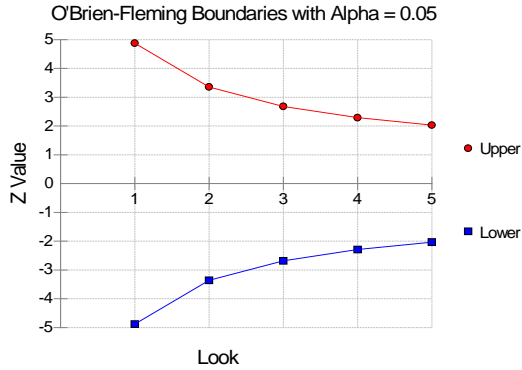
$$\alpha(1) = \alpha$$

The last characteristic guarantees a fixed α level when the trial is complete. This methodology is very flexible since neither the times nor the number of analyses must be specified in advance. Only the functional form of $\alpha(\tau)$ must be specified.

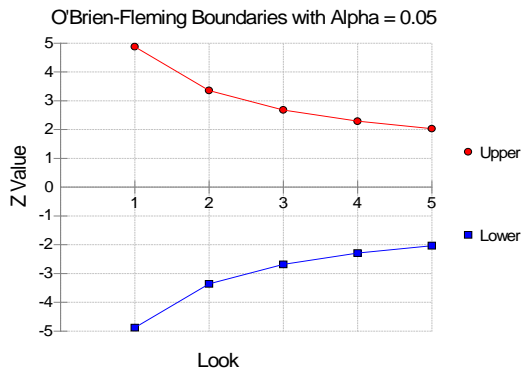
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PASS provides several popular spending functions plus the ability to enter and analyze your own percents of alpha or beta spent. These are calculated as follows (beta may be substituted for alpha for beta-spending functions):

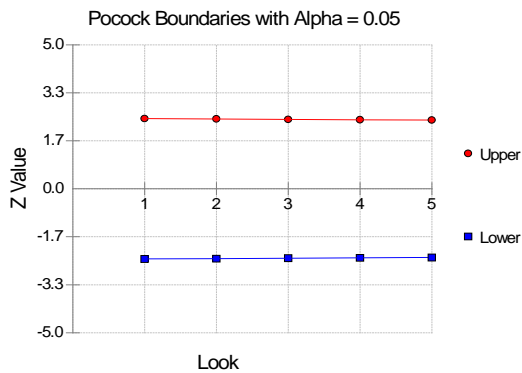
- Hwang-Shih-DeCani (gamma family)** $\alpha \left[\frac{1-e^{-\gamma t}}{1-e^{-\gamma}} \right], \gamma \neq 0; \alpha t, \gamma = 0$



- O'Brien-Fleming Analog** $2 - 2\Phi\left(\frac{Z_{\alpha/2}}{\sqrt{t}}\right)$

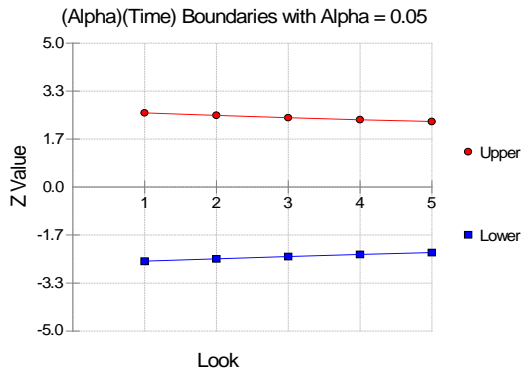


- Pocock Analog** $\alpha \cdot \ln(1 + (e - 1)t)$

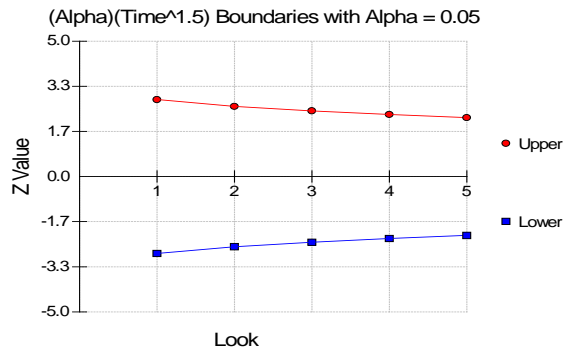


Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

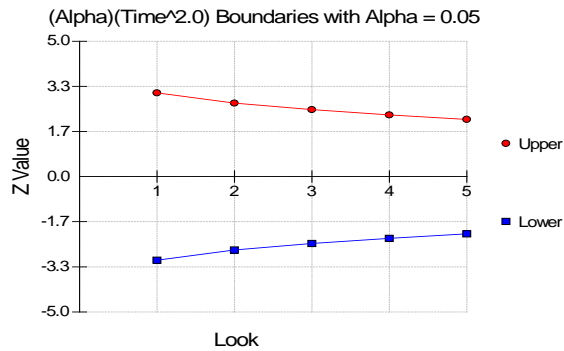
4. Alpha * time $\alpha \cdot t$



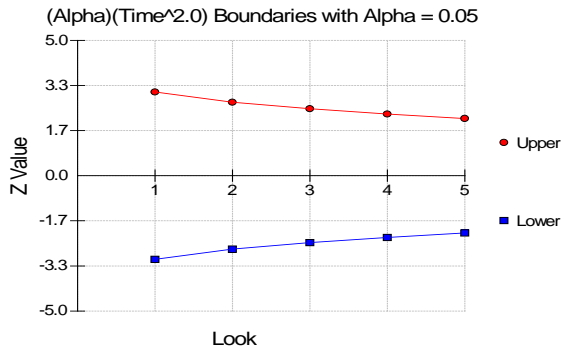
5. Alpha * time^1.5 $\alpha \cdot t^{3/2}$



6. Alpha * time^2 $\alpha \cdot t^2$



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7. Alpha * time^C $\alpha \cdot t^C$ 

8. User Supplied Percents

A custom set of percents of alpha to be spent at each look may be input directly.

The O'Brien-Fleming Analog spends very little alpha or beta at the beginning and much more at the final looks. The Pocock Analog and (Alpha or Beta)(Time) spending functions spend alpha or beta more evenly across the looks. The Hwang-Shih-DeCani (C) (gamma family) spending functions and (Alpha or Beta)(Time^C) spending functions are flexible spending functions that can be used to spend more alpha or beta early or late or evenly, depending on the choice of C.

Example 1 – Power and Output

A clinical trial is to be conducted over a two-year period to compare the proportion response of a new treatment to that of the current treatment. The current response proportion is 0.58. The researchers would like to show that the new treatment is at least 92% as effective as the old treatment. Although the researchers do not know the true proportion of patients that will survive with the new treatment, they would like to examine the power that is achieved if the proportion under the new treatment is also 0.58 (rate ratio of 1.0). The sample size at the final look is to be 1000 per group. Testing will be done at the 0.05 significance level. A total of five tests are going to be performed on the data as they are obtained. The O'Brien-Fleming (Analog) boundaries will be used.

Find the power and test boundaries assuming equal sample sizes per arm.

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
Test Type	Likelihood Score (Farr. & Mann.)
Higher Proportions Are	Better
Simulations	100000
Random Seed	4975605 (for Reproducibility)
Alpha	0.05
Group Allocation	Equal (N1 = N2)
Sample Size Per Group	1000
R0 (Non-Inferiority Ratio)	0.92
R1 (Actual Ratio)	1.0
P2 (Group 2 Proportion)	0.58

Looks & Boundaries Tab

Specification of Looks and Boundaries	Simple
Number of Equally Spaced Looks	5
Alpha Spending Function	O'Brien-Fleming Analog
Type of Futility Boundary	None

Output

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

Scenario 1 Numeric Results for Group Sequential Testing Proportion Ratio = NIR.

Solve For: [Power](#)
 Hypotheses: H0: Proportion 1 / Proportion 2 = NIR; H1: Proportion 1 / Proportion 2 > NIR
 Test Statistic: Likelihood Score (Farrington and Manning) Test
 Zero Adjustment Method: None
 Alpha-Spending Function: O'Brien-Fleming Analog
 Beta-Spending Function: None
 Futility Boundary Type: None
 Number of Looks: 5
 Simulations: 100000
 Random Seed: 4975605 (User-Entered)

Numeric Summary for Scenario 1

Value	Power		Alpha				Beta
	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
0.691	0.688	0.694	0.05	0.05	0.048	0.051	0.309

		Average Sample Size								
N1	N2	Given H0		Given H1		R0	R1	P1.0	P1.1	P2
		Grp1	Grp2	Grp1	Grp2					
1000	1000	992	992	830	830	0.92	1	0.53	0.58	0.58

Power: The probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.

Power 95% LCL and UCL: The lower and upper confidence limits for the power estimate. The width of the interval is based on the number of simulations.

Target Alpha: The user-specified probability of rejecting a true null hypothesis. It is the total alpha spent.

Alpha or Actual Alpha: The alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.

Alpha 95% LCL and UCL: The lower and upper confidence limits for the actual alpha estimate. The width of the interval is based on the number of simulations.

Beta: The probability of accepting a false null hypothesis. It is the total proportion of alternative hypothesis simulations that do not cross the significance boundaries.

N1 and N2: The sample sizes of each group if the study reaches the final look.

Average Sample Size Given H0: The average or expected sample sizes of each group if H0 is true. These are based on the proportion of null hypothesis simulations that cross the significance or futility boundaries at each look.

Average Sample Size Given H1: The average or expected sample sizes of each group if H1 is true. These are based on the proportion of alternative hypothesis simulations that cross the significance or futility boundaries at each look.

R0: The non-inferiority ratio is the proportion ratio between groups (Grp1 / Grp2) assuming the null hypothesis, H0.

R1: The proportion ratio between groups (Grp1 / Grp2) assuming the alternative hypothesis, H1.

P1.0: The proportion used in the simulations for Group 1 under H0.

P1.1: The proportion used in the simulations for Group 1 under H1.

P2: The proportion used in the simulations for Group 2 under H0 and H1.

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Summary Statements

A group sequential trial with sample sizes of 1000 and 1000 at the final look achieve 69% power to detect a ratio of 1 of the treatment group proportion to a control group proportion of 0.58 with a non-inferiority ratio of 0.92 with an overall Type I error rate (α) of 0.05 using a one-sided Likelihood Score (Farrington and Manning) Test.

Accumulated Information Details for Scenario 1

Look	Accumulated Information Percent	Accumulated Sample Size		
		Group 1	Group 2	Total
1	20	200	200	400
2	40	400	400	800
3	60	600	600	1200
4	80	800	800	1600
5	100	1000	1000	2000

Look	The number of the look.
Accumulated Information Percent	The percent of the sample size accumulated up to the corresponding look.
Accumulated Sample Size Group 1	The total number of individuals in group 1 at the corresponding look.
Accumulated Sample Size Group 2	The total number of individuals in group 2 at the corresponding look.
Accumulated Sample Size Total	The total number of individuals in the study (group 1 + group 2) at the corresponding look.

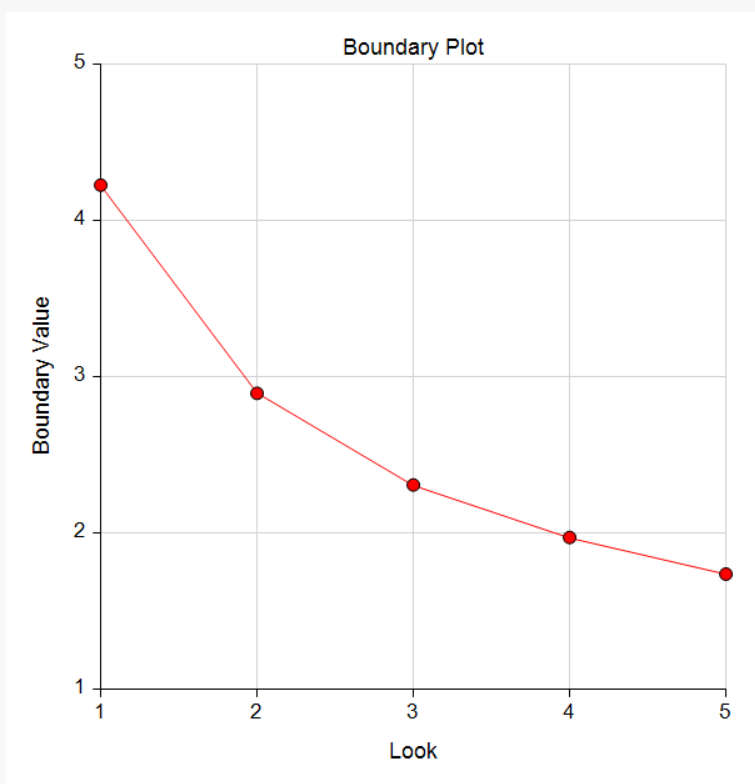
Boundaries for Scenario 1

Look	Significance Boundary	
	Z-Value Scale	P-Value Scale
1	4.22678	0.00001
2	2.89402	0.00190
3	2.30764	0.01051
4	1.97162	0.02433
5	1.73725	0.04117

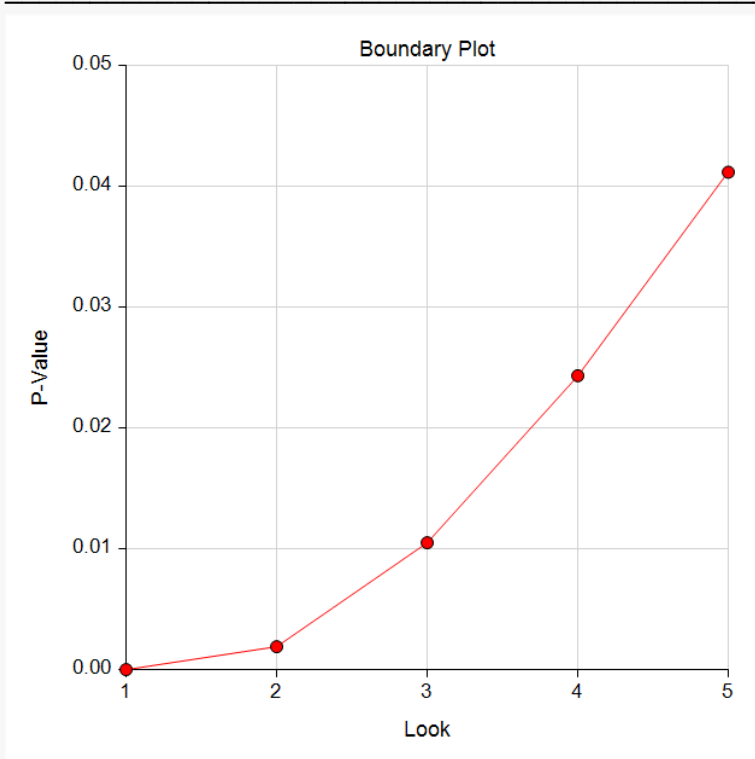
Look	The number of the look.
Significance Boundary Z-Value Scale	The value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.
Significance Boundary P-Value Scale	The value such that P-Values outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. This P-Value corresponds to the Z-Value Boundary and is sometimes called the nominal alpha.

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Boundary Plot



Boundary Plot - P-Value



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Significance Boundaries with 95% Simulation Confidence Intervals for Scenario 1

Look	Z-Value Boundary			P-Value Boundary		
	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	4.22678			0.00001		
2	2.89402	2.85755	2.94640	0.00190	0.00161	0.00213
3	2.30764	2.28678	2.32224	0.01051	0.01011	0.01110
4	1.97162	1.95790	1.99429	0.02433	0.02306	0.02512
5	1.73725	1.72649	1.75323	0.04117	0.03978	0.04213

Look The number of the look.
 Z-Value Boundary Value The value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.
 P-Value Boundary Value The value such that P-Values outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. This P-Value corresponds to the Z-Value Boundary and is sometimes called the nominal alpha.
 95% LCL and UCL The lower and upper confidence limits for the boundary at the given look. The width of the interval is based on the number of simulations.

Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

Look	Signif. Boundary		Target		Actual		Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
	Z-Value Scale	P-Value Scale	Spending Function Alpha	Cum. Spending Function Alpha	Alpha Spent	Cum. Alpha Spent		
1	4.22678	0.00001	0.000	0.000	0.000	0.000	0.001	0.001
2	2.89402	0.00190	0.002	0.002	0.002	0.002	0.066	0.066
3	2.30764	0.01051	0.009	0.011	0.009	0.011	0.210	0.276
4	1.97162	0.02433	0.017	0.028	0.017	0.028	0.232	0.508
5	1.73725	0.04117	0.022	0.050	0.022	0.050	0.183	0.691

Look The number of the look.
 Significance Boundary Z-Value Scale The value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.
 Significance Boundary P-Value Scale The value such that P-Values outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. This P-Value corresponds to the Significance Z-Value Boundary and is sometimes called the nominal alpha.
 Spending Function Alpha The intended portion of alpha allocated to the particular look based on the alpha-spending function.
 Cumulative Spending Function Alpha The intended accumulated alpha allocated to the particular look. It is the sum of the Spending Function Alpha up to the corresponding look.
 Alpha Spent The proportion of the null hypothesis simulations resulting in statistics outside the Significance Boundary at this look.
 Cumulative Alpha Spent The proportion of the null hypothesis simulations resulting in Significance Boundary termination up to and including this look. It is the sum of the Alpha Spent up to the corresponding look.
 Proportion H1 Sims Outside Significance Boundary The proportion of the alternative hypothesis simulations resulting in statistics outside the Significance Boundary at this look. It may be thought of as the incremental power.
 Cumulative H1 Sims Outside Significance Boundary The proportion of the alternative hypothesis simulations resulting in Significance Boundary termination up to and including this look. It is the sum of the Proportion H1 Sims Outside Significance Boundary up to the corresponding look.

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Numeric Results for Group Sequential Testing Proportion Ratio = NIR.

Solve For: [Power](#)
 Hypotheses: H0: Proportion 1 / Proportion 2 = NIR; H1: Proportion 1 / Proportion 2 > NIR
 Test Statistic: Likelihood Score (Farrington and Manning) Test
 Zero Adjustment Method: None
 Alpha-Spending Function: O'Brien-Fleming Analog
 Beta-Spending Function: None
 Futility Boundary Type: None
 Number of Looks: 5
 Simulations: 100000
 Random Seed: 4975605 (User-Entered)

Numeric Summary of Scenarios

Scenario	Power	N1	N2	Alpha	R0	R1	P1.0	P1.1	P2
1	0.691	1000	1000	0.05	0.92	1	0.53	0.58	0.58

Power The probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.
 Alpha The alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.
 N1 and N2 The sample sizes of each group if the study reaches the final look.
 R0 The non-inferiority ratio is the proportion ratio between groups (Grp1 / Grp2) assuming the null hypothesis, H0.
 R1 The proportion ratio between groups (Grp1 / Grp2) assuming the alternative hypothesis, H1.
 P1.0 The proportion used in the simulations for Group 1 under H0.
 P1.1 The proportion used in the simulations for Group 1 under H1.
 P2 The proportion used in the simulations for Group 2 under H0 and H1.

Power and Alpha Summary

Scenario	Power			Alpha				Beta
	Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
1	0.691	0.688	0.694	0.05	0.05	0.048	0.051	0.309

Power The probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.
 Power 95% LCL and UCL The lower and upper confidence limits for the power estimate. The width of the interval is based on the number of simulations.
 Target Alpha The user-specified probability of rejecting a true null hypothesis. It is the total alpha spent.
 Alpha or Actual Alpha The alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.
 Alpha 95% LCL and UCL The lower and upper confidence limits for the actual alpha estimate. The width of the interval is based on the number of simulations.
 Beta The probability of accepting a false null hypothesis. It is the total proportion of alternative hypothesis simulations that do not cross the significance boundaries.

Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

Sample Size Summary

Scenario	Power	Alpha	N1	N2	Average Sample Size			
					Given H0		Given H1	
					Grp1	Grp2	Grp1	Grp2
1	0.691	0.05	1000	1000	992	992	830	830

Power The probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.

Alpha The alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.

N1 and N2 The sample sizes of each group if the study reaches the final look.

Average Sample Size Given H0 The average or expected sample sizes of each group if H0 is true. These are based on the proportion of null hypothesis simulations that cross the significance or futility boundaries at each look.

Average Sample Size Given H1 The average or expected sample sizes of each group if H1 is true. These are based on the proportion of alternative hypothesis simulations that cross the significance or futility boundaries at each look.

References

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

The values obtained from any given run of this example will vary slightly due to the variation in simulations.

Example 2 – Power with Futility Boundaries

Continuing with Example 1, suppose that the researchers would also like to terminate the study early if there is indication that the treatment is not non-inferior.

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	Power
Test Type.....	Likelihood Score (Farr. & Mann.)
Higher Proportions Are	Better
Simulations	100000
Random Seed.....	Blank or Random
Alpha.....	0.05
Group Allocation	Equal (N1 = N2)
Sample Size Per Group	1000
R0 (Non-Inferiority Ratio).....	0.92
R1 (Actual Ratio)	1.0
P2 (Group 2 Proportion).....	0.58

Looks & Boundaries Tab

Specification of Looks and Boundaries	Simple
Number of Equally Spaced Looks.....	5
Alpha Spending Function.....	O'Brien-Fleming Analog
Type of Futility Boundary	Non-Binding
Number of Skipped Futility Looks	0
Beta Spending Function.....	O'Brien-Fleming Analog

Output

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

Scenario 1 Numeric Results for Group Sequential Testing Proportion Ratio = NIR.

Solve For: [Power](#)
 Hypotheses: H0: Proportion 1 / Proportion 2 = NIR; H1: Proportion 1 / Proportion 2 > NIR
 Test Statistic: Likelihood Score (Farrington and Manning) Test
 Zero Adjustment Method: None
 Alpha-Spending Function: O'Brien-Fleming Analog
 Beta-Spending Function: O'Brien-Fleming Analog
 Futility Boundary Type: Non-Binding
 Number of Looks: 5
 Simulations: 100000
 Random Seed: 5643032 (Computer-Generated)

Numeric Summary for Scenario 1

Value	Power		Alpha				Beta
	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	
0.581	0.578	0.584	0.05	0.037	0.036	0.038	0.419

Average Sample Size										
N1	N2	Given H0		Given H1		R0	R1	P1.0	P1.1	P2
		Grp1	Grp2	Grp1	Grp2					
1000	1000	431	431	648	648	0.92	1	0.53	0.58	0.58

Accumulated Information Details for Scenario 1

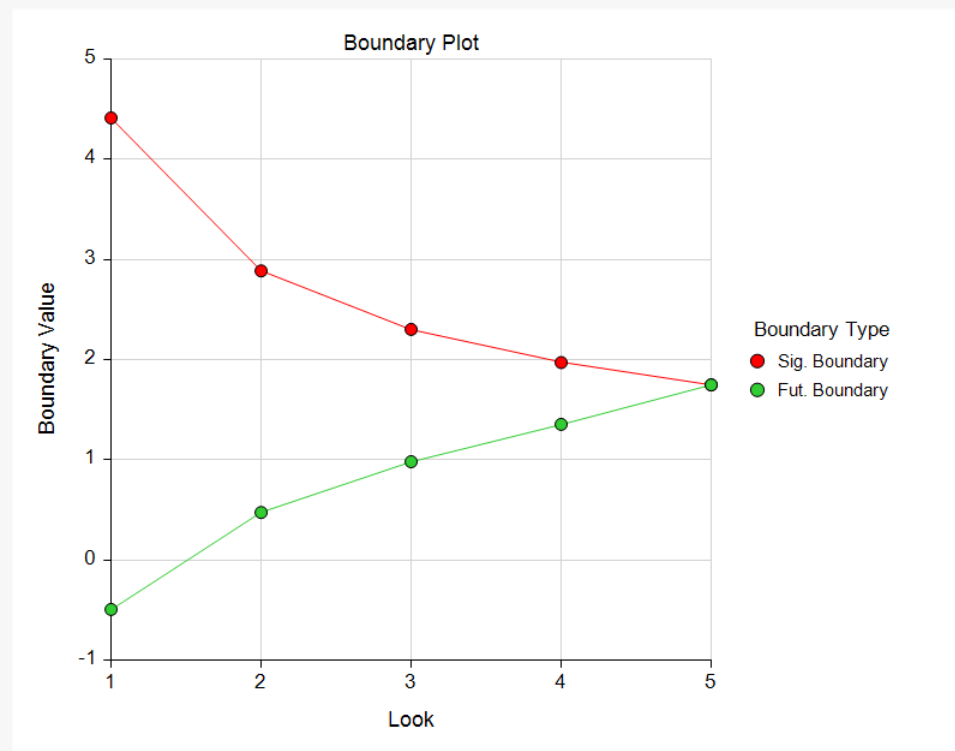
Look	Accumulated Information Percent	Accumulated Sample Size		
		Group 1	Group 2	Total
1	20	200	200	400
2	40	400	400	800
3	60	600	600	1200
4	80	800	800	1600
5	100	1000	1000	2000

Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

Boundaries for Scenario 1

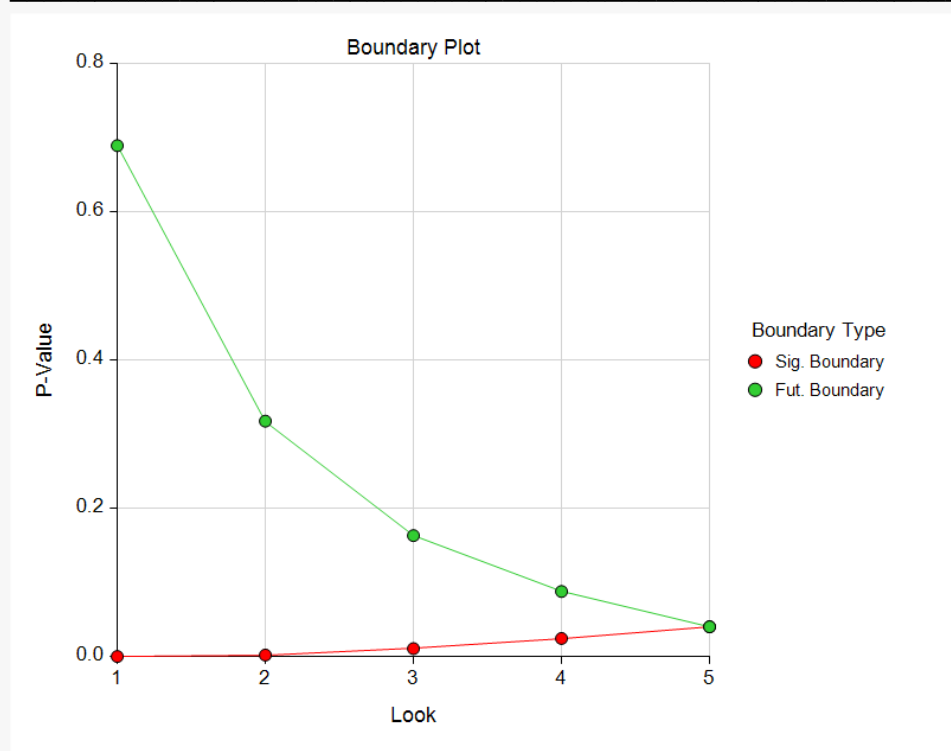
Look	Significance Boundary		Futility Boundary	
	Z-Value Scale	P-Value Scale	Z-Value Scale	P-Value Scale
1	4.41382	0.00001	-0.49364	0.68922
2	2.88650	0.00195	0.47467	0.31751
3	2.30249	0.01065	0.98152	0.16317
4	1.97162	0.02433	1.35455	0.08778
5	1.74932	0.04012	1.74932	0.04012

Boundary Plot



Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

Boundary Plot - P-Value



Significance Boundaries with 95% Simulation Confidence Intervals for Scenario 1

Look	Z-Value Boundary			P-Value Boundary		
	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	4.41382			0.00001		
2	2.88650	2.84195	2.93283	0.00195	0.00168	0.00224
3	2.30249	2.28098	2.31899	0.01065	0.01020	0.01127
4	1.97162	1.95626	1.99013	0.02433	0.02329	0.02522
5	1.74932	1.73578	1.76530	0.04012	0.03876	0.04130

Futility Boundaries with 95% Simulation Confidence Intervals for Scenario 1

Look	Z-Value Boundary			P-Value Boundary		
	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	-0.49364	-0.50654	-0.48433	0.68922		
2	0.47467	0.46298	0.48218	0.31751	0.31484	0.32169
3	0.98152	0.97053	0.98833	0.16317	0.16150	0.16589
4	1.35455	1.34513	1.36036	0.08778	0.08686	0.08929
5	1.74932	1.74418	1.76163	0.04012	0.03907	0.04056

Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

Look	Signif. Boundary		Target		Actual		Proportion H0 Sims Outside Futility Boundary	Cum. H0 Sims Outside Futility Boundary
	Z-Value Scale	P-Value Scale	Spending Function Alpha	Cum. Spending Function Alpha	Alpha Spent	Cum. Alpha Spent		
	1	4.41382	0.00001	0.000	0.000	0.000		
2	2.88650	0.00195	0.002	0.002	0.002	0.002	0.390	0.700
3	2.30249	0.01065	0.009	0.011	0.009	0.011	0.162	0.862
4	1.97162	0.02433	0.017	0.028	0.015	0.026	0.071	0.933
5	1.74932	0.04012	0.022	0.050	0.011	0.037	0.030	0.963

Beta-Spending and Alternative Hypothesis Simulation Details for Scenario 1

Look	Futility Boundary		Target		Actual		Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
	Z-Value Scale	P-Value Scale	Spending Function Beta	Cum. Spending Function Beta	Beta Spent	Cum. Beta Spent		
	1	-0.49364	0.68922	0.071	0.071	0.071		
2	0.47467	0.31751	0.131	0.202	0.131	0.202	0.066	0.066
3	0.98152	0.16317	0.096	0.298	0.096	0.298	0.208	0.274
4	1.35455	0.08778	0.069	0.367	0.069	0.367	0.207	0.481
5	1.74932	0.04012	0.053	0.420	0.052	0.419	0.100	0.581

The values obtained from any given run of this example will vary slightly due to the variation in simulations.

Example 3 – Enter Boundaries

With a set-up similar to Example 2, suppose we wish to investigate the properties of a set of significance (3, 3, 3, 2, 1) and futility (-2, -1, 0, 0, 1) boundaries.

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	Alpha and Power (Enter Boundaries)
Test Type.....	Likelihood Score (Farr. & Mann.)
Higher Proportions Are	Better
Simulations	100000
Random Seed.....	Blank or Random
Group Allocation	Equal (N1 = N2)
Sample Size Per Group	1000
R0 (Non-Inferiority Ratio).....	0.92
R1 (Actual Ratio)	1.0
P2 (Group 2 Proportion).....	0.58

Looks & Boundaries Tab

Number of Looks	5
Equally Spaced.....	Checked
Types of Boundaries	Significance and Futility Boundaries
Significance Boundary	3 3 3 2 1 (for looks 1 through 5)
Futility Boundary	-2 -1 0 0 1 (for looks 1 through 5)

Output

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

Scenario 1 Numeric Results for Group Sequential Testing Proportion Ratio = NIR.

Solve For: [Alpha and Power \(Enter Boundaries\)](#)
 Hypotheses: H0: Proportion 1 / Proportion 2 = NIR; H1: Proportion 1 / Proportion 2 > NIR
 Test Statistic: Likelihood Score (Farrington and Manning) Test
 Zero Adjustment Method: None
 Type of Boundaries: Significance and Futility Boundaries
 Number of Looks: 5
 Simulations: 100000
 Random Seed: 5676124 (Computer-Generated)

Numeric Summary for Scenario 1

Power			Alpha			Beta
Value	95% LCL	95% UCL	Value	95% LCL	95% UCL	
0.867	0.865	0.869	0.151	0.149	0.153	0.133

Average Sample Size										
N1	N2	Given H0		Given H1		R0	R1	P1.0	P1.1	P2
		Grp1	Grp2	Grp1	Grp2					
1000	1000	738	738	838	838	0.92	1	0.53	0.58	0.58

Accumulated Information Details for Scenario 1

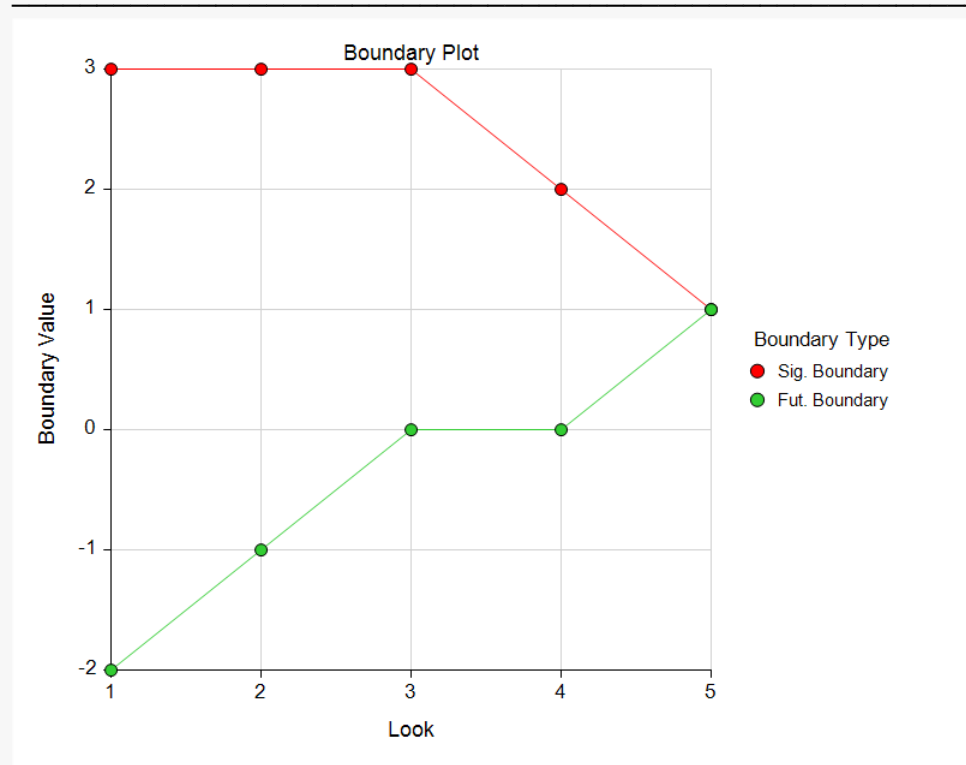
Look	Accumulated Information Percent	Accumulated Sample Size		
		Group 1	Group 2	Total
1	20	200	200	400
2	40	400	400	800
3	60	600	600	1200
4	80	800	800	1600
5	100	1000	1000	2000

Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

Boundaries for Scenario 1

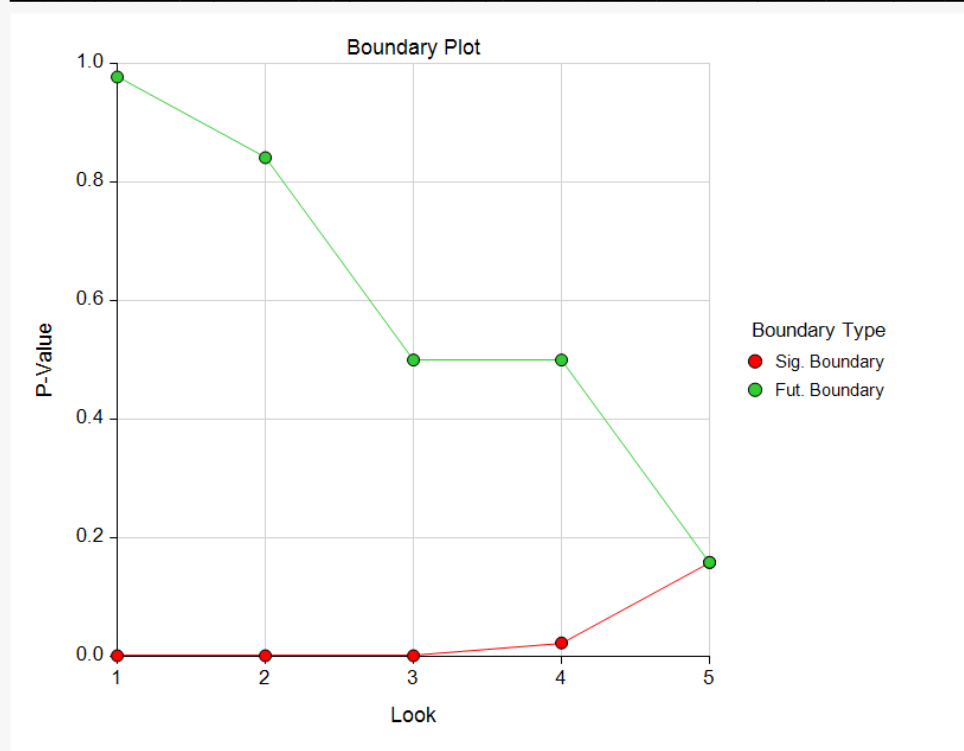
Look	Significance Boundary		Futility Boundary	
	Z-Value Scale	P-Value Scale	Z-Value Scale	P-Value Scale
1	3	0.00135	-2	0.97725
2	3	0.00135	-1	0.84134
3	3	0.00135	0	0.50000
4	2	0.02275	0	0.50000
5	1	0.15866	1	0.15866

Boundary Plot



Group-Sequential Non-Inferiority Tests for the Ratio of Two Proportions (Simulation)

Boundary Plot - P-Value



Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

Look	Signif. Boundary		Alpha Spent	Cum. Alpha Spent	Proportion H0 Sims Outside Futility Boundary	Cum. H0 Sims Outside Futility Boundary
	Z-Value Scale	P-Value Scale				
1	3	0.00135	0.001	0.001	0.022	0.022
2	3	0.00135	0.001	0.003	0.138	0.160
3	3	0.00135	0.001	0.003	0.346	0.507
4	2	0.02275	0.021	0.024	0.082	0.588
5	1	0.15866	0.127	0.151	0.261	0.849

Beta-Spending and Alternative Hypothesis Simulation Details for Scenario 1

Look	Futility Boundary		Beta Spent	Cum. Beta Spent	Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
	Z-Value Scale	P-Value Scale				
1	-2	0.97725	0.002	0.002	0.023	0.023
2	-1	0.84134	0.008	0.010	0.042	0.065
3	0	0.50000	0.039	0.049	0.055	0.121
4	0	0.50000	0.007	0.056	0.364	0.485
5	1	0.15866	0.077	0.133	0.382	0.867

The values obtained from any given run of this example will vary slightly due to the variation in simulations.

Example 4 – Validation using Simulation

With a set-up similar to Example 2, we examine the power and alpha generated by the set of significance (4.54627, 2.88975, 2.31861, 1.97055, 1.74852) and futility (-0.50654, 0.46847, 0.97760, 1.34640, 1.74852) boundaries.

For reproducibility, we'll use a random seed of 5485182.

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	Alpha and Power (Enter Boundaries)
Test Type.....	Likelihood Score (Farr. & Mann.)
Higher Proportions Are	Better
Simulations	100000
Random Seed.....	5485182 (for Reproducibility)
Group Allocation	Equal (N1 = N2)
Sample Size Per Group	1000
R0 (Non-Inferiority Ratio).....	0.92
R1 (Actual Ratio)	1.0
P2 (Group 2 Proportion).....	0.58

Looks & Boundaries Tab

Number of Looks	5
Equally Spaced.....	Checked
Types of Boundaries	Significance and Futility Boundaries
Significance Boundary	4.54627, 2.88975, 2.31861, 1.97055, 1.74852
Futility Boundary	-0.50654, 0.46847, 0.97760, 1.34640, 1.74852

Output

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

Scenario 1 Numeric Results for Group Sequential Testing Proportion Ratio = NIR.

Solve For: [Alpha and Power \(Enter Boundaries\)](#)
 Hypotheses: H0: Proportion 1 / Proportion 2 = NIR; H1: Proportion 1 / Proportion 2 > NIR
 Test Statistic: Likelihood Score (Farrington and Manning) Test
 Zero Adjustment Method: None
 Type of Boundaries: Significance and Futility Boundaries
 Number of Looks: 5
 Simulations: 100000
 Random Seed: 5485182 (User-Entered)

Numeric Summary for Scenario 1

Power			Alpha			Beta
Value	95% LCL	95% UCL	Value	95% LCL	95% LCL	
0.583	0.58	0.586	0.036	0.035	0.037	0.417

Average Sample Size										
N1	N2	Given H0		Given H1		R0	R1	P1.0	P1.1	P2
		Grp1	Grp2	Grp1	Grp2					
1000	1000	433	433	652	652	0.92	1	0.53	0.58	0.58

The power and alpha generated with these boundaries are very close to the values of Example 2.