Chapter 711

Group-Sequential Logrank Tests (Simulation) (Legacy)

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. Survival rates can be piece-wise customized.

Introduction

This procedure can be used to determine power, sample size and/or boundaries for group sequential tests comparing two survival curves. The tests that can be simulated in this procedure are the common logrank test, the Gehan-Wilcoxon test, the Tarone-Ware test, the Peto-Peto and Modified Peto-Peto tests, and the Fleming-Harrington tests with user specified p and q.

Survival rates (hazard rates, median survival times, proportion surviving, or mortality) can be piece-wise customized to specify proportional hazard scenarios or non-proportional hazard scenarios. The treatment group survival rates can be specified directly or based on hazard ratios (or mortality ratios).

Loss-to-follow-up and noncompliance proportions can be entered with piece-wise flexibility. Noncompliance survival rates can be specified directly or can be set to the opposite treatment group survival rate.

Accrual times and accrual patterns are completely flexible.

For two-sided tests, significance (efficacy) boundaries can be generated. For one-sided 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 also given for each boundary statistic. Plots of boundaries are also produced.

Four Different Effect Size Parameterizations

There are four closely related effect size parameterizations that are available in this procedure and documented in this chapter. The parameterization can be in terms of hazard rates, median survival times, proportions surviving a given time period, or mortality during a given time period. When median survival times, proportions surviving, or mortality are used, the values are converted to the corresponding hazard rates before the simulation process begins.

Hazard Rate Parameterization

In this case, the hazard rates for the control and treatment groups are specified directly.

Median Survival Time Parameterization

Here, the median survival time is specified. These are transformed to hazard rates using the relationship $h = \ln(2) / MST$.

Proportion Surviving Parameterization

In this case, the proportion surviving until a given time $T0$ is specified. These are transformed to hazard rates using the relationship $h = -\ln(S(T0)) / T0$. When separate proportions surviving are given for each time period, *T0* is taken to be the time period unit.

Mortality Parameterization

Here, the mortality until a given time $T0$ is specified. These are transformed to hazard rates using the relationship $h = -\ln(1 - M(T0)) / T0$. When separate mortalities are given for each time period, *T0* is taken to be the time period unit.

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. The total sample size is divided into the control and treatment group sample sizes (N1 and N2) according to the proportion in control group given.
2. Based on the specified survival rates, and noncompliance proportions and survival rates, a hazard rate function is generated for each subject of each group. The hazard rate function is used to generate a random survival time and the loss proportion is used to determine whether the simulated subject is right censored due to loss before the event. Each subject is simulated as though the final look is reached.
3. A starting time for each subject is generated based on the accrual time and the accrual pattern.

4. For each sample (of N1 + N2 subjects), a test statistic for each look is produced. Subjects for which the start time exceeds the look time are excluded at that look. Subjects with survival times or loss times after the look time are right censored at that look. For example, suppose the study length is 5 years with 5 looks, one at each year, and the accrual time is 2 years. Suppose a subject is given a start time of 0.3689 and a survival time of 2.541 years with no loss-to-follow-up. That subject would be used in all 5 looks. At the first look, the subject would be right-censored with a survival time of 1 – 0.3689. At the second look, the subject would be right-censored with a survival time of 2 – 0.3689. At the third look, the subject would be right-censored with a survival time of 3 – 0.3689. At the fourth look, the subject would not be right-censored with a survival time of 2.541 (since 2.541 < 4 – 0.3689). At the final look, the subject would again not be right censored with a survival time of 2.541.
5. To generate the first significance boundary, the null distribution statistics of the first look (e.g., at Time = 1 year) 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.
6. 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.
7. To generate the second significance boundary, the remaining null distribution statistics of the second look (e.g., at Time = 2 years) 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 970^{th} (20 in from 990) statistic is the second boundary.
8. 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 N1 = N2 = 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 100 or fewer per group, the discrete nature of the number of possible combinations of ranks in each group comes into play. This simulation procedure is based 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 some small-sample cases.

Test Statistics

This section presents methods for testing that the survival curves, and thus the hazard rates, of two or more populations are equal. The specific hypothesis set that is being tested is

$$H_0: h_1(T) = h_2(T) \text{ for all t} \leq \tau$$

$$H_1: h_1(T) \neq h_2(T) \text{ for some t} \leq \tau$$

In words, the null hypothesis is that the hazard rates of the two populations are equal at all times less than the maximum observed time and the alternative hypothesis is that the two hazard rates differ at some time less than the observed maximum time.

The general form of the test statistic is

$$Z = \frac{\sum_{i=1}^{D} W(t_i)\left[d_{i1} - Y_{i1}\left(\frac{d_i}{Y_i}\right)\right]}{\sqrt{\sum_{i=1}^{D} W(t_i)^2 \frac{Y_{i1}}{Y_i}\left(1 - \frac{Y_{i1}}{Y_i}\right)\left(\frac{Y_i - d_i}{Y_i - 1}\right) d_i}}$$

where

D is the number of distinct event times

$W(t_i)$ is the weight function at time t_i

Y_{i1} is the number at risk in the Group 1 sample at time t_i

Y_i is the combined number at risk at time t_i

d_{i1} is the number of events in the Group 1 sample at time t_i

d_i is the combined number of events at time t_i

Details of the above formulas can be found in Klein and Moeschberger (1997), pages 191-202 and Andersen, Borgan, Gill, and Keiding (1992), pages 345-356.

Six different choices for the weight function, *W*(*T*), with the flexible p and q for the Fleming-Harrington weight function, result in a variety of tests that are available in this procedure. The most commonly used test is the logrank test which has equal weighting. The other tests shift the heaviest weighting to the beginning or end of the trial. This may be appropriate in some studies, but the use of one of these other weighting schemes should be designated before the data have been seen. Because of the different weighting patterns, they will often give quite different results.

The following table describes each of these tests.

Test	**Weight**	**Comments**
Logrank	1	This is the most commonly used test. It places equal weights across all times. This test has optimum power when the hazard rates of the *K* populations are proportional to each other.
Gehan-Wilcoxon	Y_i	Places weight on hazards at the beginning of the study.
Tarone-Ware	$\sqrt{Y_i}$	Places weight on hazards at the beginning of the study.
Peto-Peto	$\tilde{S}(t_i)$	Places weight on hazards at the beginning of the study.
Modified Peto-Peto	$\tilde{S}(t_i)Y_i/(Y_i+1)$	Places weight on hazards at the beginning of the study.
Fleming-Harrington (1,0)	$\hat{S}(t_{i-1})$	Places weight on hazards at the beginning of the study.
Fleming-Harrington (0.5,0.5)	$\sqrt{\hat{S}(t_{i-1})\left(1-\hat{S}(t_{i-1})\right)}$	Places weight on hazards in the middle of the study.
Fleming-Harrington (1,1)	$\hat{S}(t_{i-1})\left(1-\hat{S}(t_{i-1})\right)$	Places weight on hazards in the middle of the study.
Fleming-Harrington (0,1)	$1-\hat{S}(t_{i-1})$	Places weight on hazards at the end of the study.
Fleming-Harrington (0.5,2)	$\sqrt{\hat{S}(t_{i-1})}\left(1-\hat{S}(t_{i-1})\right)^2$	Places weight on hazards at the end of the study.

This table uses the following definitions:

$$\hat{S}(t)=\prod_{t_i\le t}\left(1-\frac{d_i}{Y_i}\right)$$

$$\tilde{S}(t)=\prod_{t_i\le t}\left(1-\frac{d_i}{Y_i+1}\right)$$

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

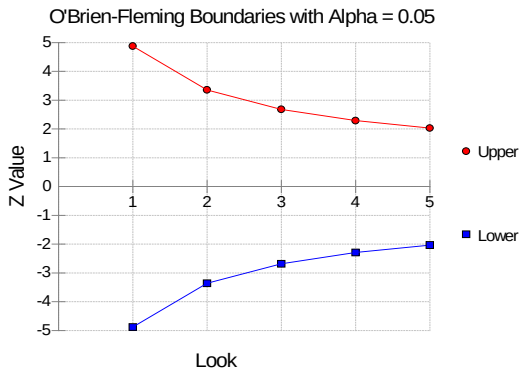
$$\alpha(0) = 0$$

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

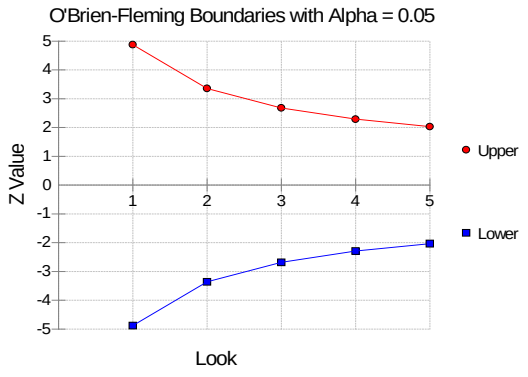
The last characteristic guarantees a fixed α level when the trial is complete. This methodology is very flexible since neither the times nor the number of analyses must be specified in advance. Only the functional form of $\alpha(\tau)$ must be specified.

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):

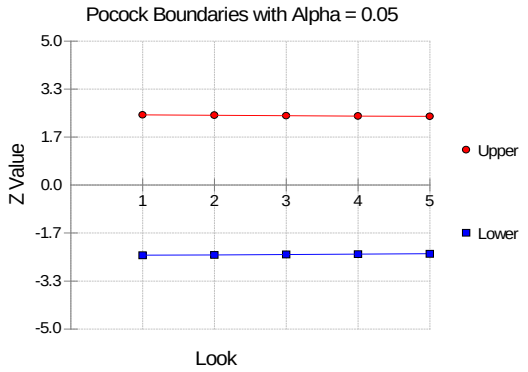
1. **Hwang-Shih-DeCani (gamma family)** $\alpha\left[\frac{1-e^{-\gamma t}}{1-e^{-\gamma}}\right], \gamma \neq 0; \quad \alpha t, \gamma = 0$



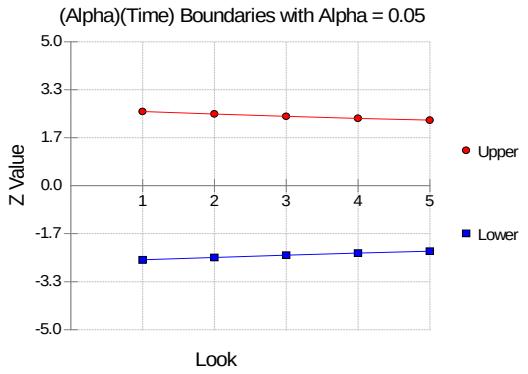
2. **O'Brien-Fleming Analog** $2 - 2\Phi\left(\frac{Z_{\alpha/2}}{\sqrt{t}}\right)$



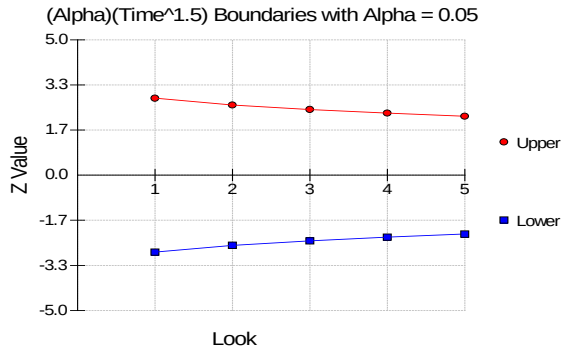
3. Pocock Analog $\alpha \cdot \ln(1 + (e - 1)t)$



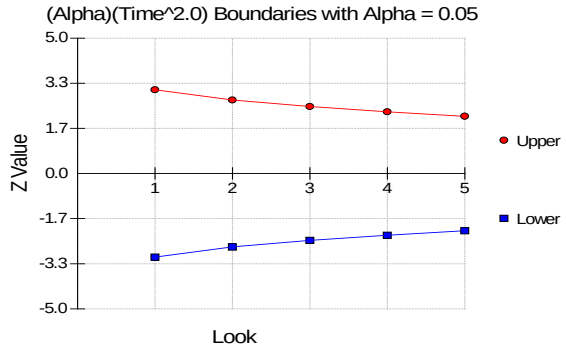
4. Alpha * time $\alpha \cdot t$



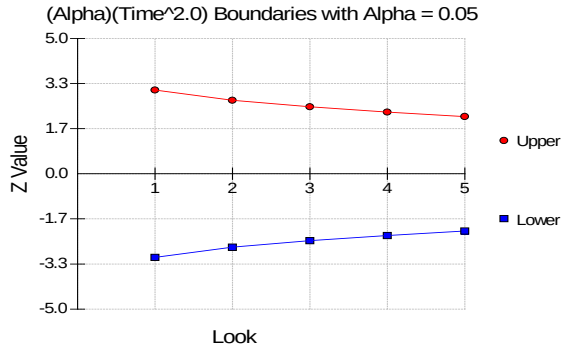
5. Alpha * time^1.5 $\alpha \cdot t^{3/2}$



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



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 five-year period to compare the survival distribution of a new treatment to that of the current treatment. The hazard rate of the current treatment is 1.4. Although the researchers do not know the true hazard rate of the new treatment, they would like to examine the power that is achieved if the hazard rate under the new treatment is 1.0. The sample size at the final look is to be 200 per group. Testing will be done at the 0.05 significance level. A total of five tests at one-year intervals are going to be performed on the data as they are obtained. All enrollees are enlisted at the beginning of the study. The O'Brien-Fleming (Analog) boundaries will be used. .

Find the power and test boundaries assuming equal sample sizes per arm and two-sided hypothesis tests.

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 1 Tab

Solve For	**Power**
Test Type	**Logrank**
Alternative Hypothesis	**H1: Hazard1 ≠ Hazard2**
Simulations	**10000**
Random Seed	**3804018** (for Reproducibility)
Alpha	**0.05**
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**200**
Percent in Group 1	**50**
Input Type	**Hazard Rate**
h1 (Hazard Rate of Control Group)	**1.4**
Treatment Group Parameter	**h2 (Hazard Rate)**
h2 (Hazard Rate of Treatment Group)	**1.0**

Design 2 Tab

Controls Lost	**0**
Treatments Lost	**0**
For Treatments Lost under H0, use	**Controls Lost**
Noncompliance Proportion (Control)	**0**
NCh1 (Noncompliance Hazard, Control)	**1.0**
At time of noncompliance, start NCh1 at	**Current time**
Noncompliance Proportion (Treatment)	**0**
NCh2 (Noncompliance Hazard, Treatment)	**1.0**
At time of noncompliance, start NCh2 at	**Current time**
For Treatment Noncomp. under H0, use	**Control Noncompliance**
Accrual Time (Integers Only)	**0**
Accrual Pattern	**Equal (Uniform)**
Total Time (Integers Only)	**5**

Looks & Boundaries Tab

Specification of Looks and Boundaries.....**Simple**
Number of Equally Spaced Looks.....**5**
Alpha 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 Hazard 1 = Hazard 2.

Solve For:	Power
Hypotheses:	H0: Hazard1 = Hazard2; H1: Hazard1 ≠ Hazard2
Test Statistic:	Logrank Test
Alpha-Spending Function:	O'Brien-Fleming Analog
Beta-Spending Function:	None
Futility Boundary Type:	None
Number of Looks:	5
Simulations:	10000
Pool Size:	20000
Random Seed:	3804018 (User-Entered)

Numeric Summary for Scenario 1

Power			Alpha				
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
0.637	0.627	0.646	0.05	0.051	0.046	0.055	0.364

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.714	1.4	1	0	Equal	5

Noncompliance					
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0	0	0	1	0	1

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.
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.
HR	The hazard ratio at which power is computed. HR = h2/h1.
h1	The hazard rate of the control group. It is the hazard rate that is simulated for both groups under H0, and for group 1 under H1.
h2	The hazard rate of the treatment group. It is the hazard rate that is simulated for group 2 under H1.
Accrual Time	The time during which subjects are enlisted into the study. It is sometimes known as the enlistment period or recruitment period.
Accrual Pattern	Describes the distribution of accrual across the Accrual Time.
Total Time	The total length of the study. It is the sum of the accrual time and the follow-up time.
Loss1 and Loss2	The loss rates (lost to follow-up and right censored) for the control and treatment groups, respectively.
Noncompliance Proportion 1 and 2	The proportion noncompliant in each time period for the control and treatment groups, respectively.
Noncompliance h1 and h2	The noncompliance hazard rates for the control and treatment groups, respectively.

Whole Study Averages

Study Length		Cum. Subject Time			
		H0		H1	
H0	H1	G1	G2	G1	G2
5	3.9	71.3	71.4	69.8	94.9

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100	100	100	100	99.9	99.9	97.7	95.1

Whole Study Averages	H0 and H1 refer to the simulations under the null and alternative hypotheses, respectively.
G1 and G2	Refer to the simulations for Groups 1 and 2, respectively.
Study Length	The average length of the study across all simulations. This length includes accrual time and follow-up time.
Cumulative Subject Time	The average total time of subject involvement. It is the average sum of survival times, including event survival times and censored survival times.
Sample size	The average number of subjects entering the study before study termination. If looks are made only after the full accrual period, these values will equal N1 and N2.
Events	The average number of events in the study before study termination.

Summary Statements

Group sequential trials with group sample sizes of 100 and 100 at the final look achieve 64% power to detect a hazard ratio of 0.714 at the 0.051 significance level (alpha) using a two-sided Logrank Test.

Detailed Input

Time Period	Accrual Pattern	Control Hazard Rate h1	Trt Hazard Rate h2	Control Loss Ls1	Trt Loss Ls2	NComp Prop Control NCP1	NComp Hazard Control NCh1	NComp Prop Trt NCP2	NComp Hazard Trt NCh2
1	100% Accrual	1.4	1	0	0	0	1	0	1
2	100% Accrual	1.4	1	0	0	0	1	0	1
3	100% Accrual	1.4	1	0	0	0	1	0	1
4	100% Accrual	1.4	1	0	0	0	1	0	1
5	100% Accrual	1.4	1	0	0	0	1	0	1

Look Details for Scenario 1

		Sample Size		Events				Cum. Subject Time	
Look	Time	Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	1	100	100	75.3	75.3	63.3	63.3	53.8	63.2
2	2	100	100	93.9	93.9	86.5	86.5	67.1	86.4
3	3	100	100	98.5	98.5	95.1	95.1	70.4	94.9
4	4	100	100	99.6	99.6	98.2	98.2	71.2	98.0
5	5	100	100	99.9	99.9	99.3	99.3	71.4	99.2

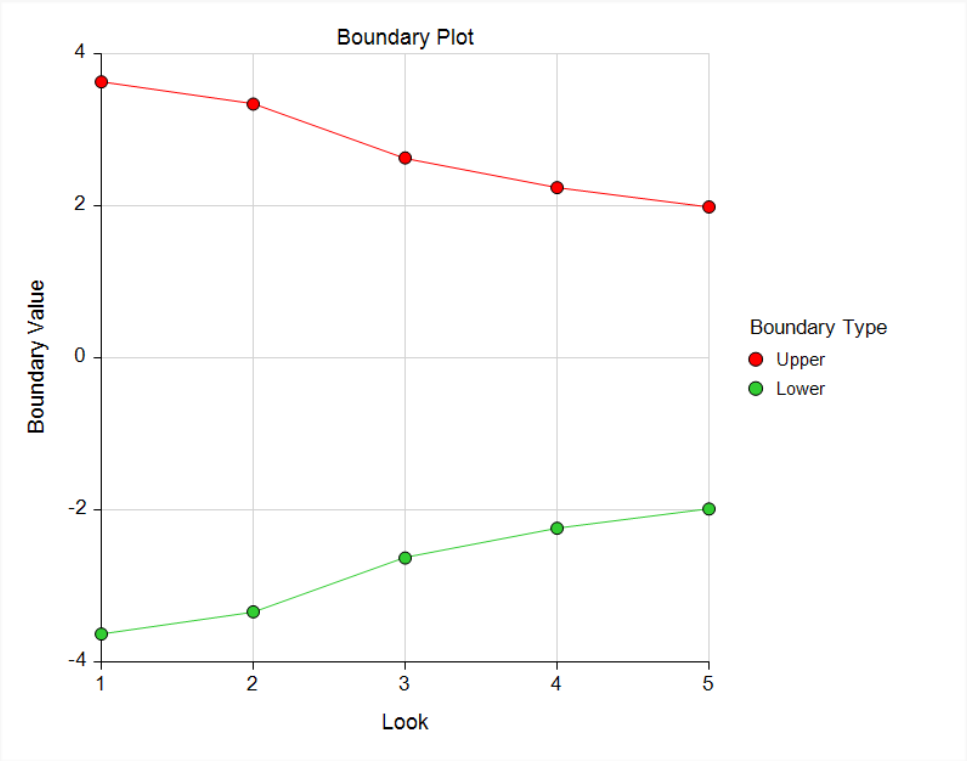
Look	The number of the look.
Time	The Time of the look from the beginning of the study (i.e., the beginning of the accrual period).
Sample Size Group 1	The average number of individuals in the control group that have entered the study by the corresponding look. If looks are made only after the full accrual period, these values will equal N1.
Sample Size Group 2	The average number of individuals in the treatment group that have entered the study by the corresponding look. If looks are made only after the full accrual period, these values will equal N2.
Events Group 1	The average number of events in the control group up to the corresponding look.
% of S.S.	The average percent of the control group sample size for which an event has occurred up to the corresponding look. It is Group 1 Events / Group 1 Sample Size.
Events Group 2	The average number of events in the treatment group up to the corresponding look.
% of S.S.	The average percent of the treatment group sample size for which an event has occurred up to the corresponding look. It is Group 2 Events / Group 2 Sample Size.
Cumulative Subject Time	The average total time of subject involvement up to the corresponding look for the control and treatment groups. It is the average sum of survival times, including event survival times and censored survival times.

Boundaries for Scenario 1

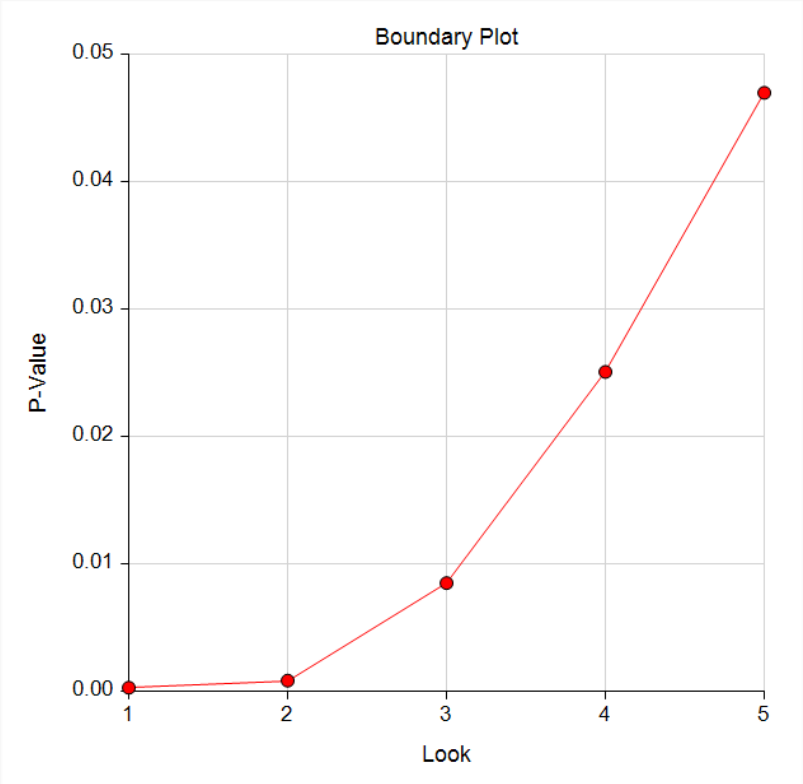
	Significance Boundary	
Look	Z-Value Scale	P-Value Scale
1	+/- 3.632	0.000
2	+/- 3.339	0.001
3	+/- 2.632	0.008
4	+/- 2.24	0.025
5	+/- 1.987	0.047

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.

Boundary Plot



Boundary Plot - P-Value



Significance Boundaries with 95% Simulation Confidence Intervals for Scenario 1

	Z-Value Boundary			P-Value Boundary		
Look	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	+/- 3.632			0.000		
2	+/- 3.339	3.028	3.773	0.001	0.000	0.002
3	+/- 2.632	2.588	2.788	0.008	0.005	0.010
4	+/- 2.24	2.192	2.305	0.025	0.021	0.028
5	+/- 1.987	1.959	2.032	0.047	0.042	0.050

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

	Signif. Boundary		Target		Actual			
Look	Z-Value Scale	P-Value Scale	Spending Function Alpha	Cum. Spending Function Alpha	Alpha Spent	Cum. Alpha Spent	Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
1	+/- 3.632	0.000	0.000	0.000	0.000	0.000	0.050	0.050
2	+/- 3.339	0.001	0.001	0.001	0.001	0.001	0.098	0.148
3	+/- 2.632	0.008	0.007	0.008	0.008	0.009	0.231	0.379
4	+/- 2.24	0.025	0.017	0.024	0.017	0.027	0.159	0.538
5	+/- 1.987	0.047	0.026	0.050	0.024	0.051	0.099	0.637

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.

Numeric Results for Group Sequential Testing Hazard 1 = Hazard 2.

Solve For:	Power
Hypotheses:	H0: Hazard1 = Hazard2; H1: Hazard1 ≠ Hazard2
Test Statistic:	Logrank Test
Alpha-Spending Function:	O'Brien-Fleming Analog
Beta-Spending Function:	None
Futility Boundary Type:	None
Number of Looks:	5
Simulations:	10000
Pool Size:	20000
Random Seed:	3804018 (User-Entered)

Numeric Summary of Scenarios

Scenario	Power	N1	N2	Alpha	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
1	0.637	100	100	0.051	0.714	1.4	1	0	Equal	5

Loss and Noncompliance Summary of Scenarios

			Noncompliance			
Scenario	Loss1	Loss2	Rate 1	h1	Rate 2	h2
1	0	0	0	1	0	1

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.
HR	The hazard ratio at which power is computed. HR = h2/h1.
h1	The hazard rate of the control group. It is the hazard rate that is simulated for both groups under H0, and for group 1 under H1.
h2	The hazard rate of the treatment group. It is the hazard rate that is simulated for group 2 under H1.
Accrual Time	The time during which subjects are enlisted into the study. It is sometimes known as the enlistment period or recruitment period.
Accrual Pattern	Describes the distribution of accrual across the Accrual Time.
Total Time	The total length of the study. It is the sum of the accrual time and the follow-up time.
Loss1 and Loss2	The loss rates (lost to follow-up and right censored) for the control and treatment groups, respectively.
Noncompliance Proportion 1 and 2	The proportion noncompliant in each time period for the control and treatment groups, respectively.
Noncompliance h1 and h2	The noncompliance hazard rates for the control and treatment groups, respectively.

Power and Alpha Summary

	Power			Alpha				
Scenario	Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
1	0.637	0.627	0.646	0.05	0.051	0.046	0.055	0.364

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.

Sample Size Summary

					Average Sample Size			
					Given H0		Given H1	
Scenario	Power	Alpha	N1	N2	Grp1	Grp2	Grp1	Grp2
1	0.637	0.051	100	100	5	3.9	0	5

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

Klein, J.P., Moeschberger, M.L.. 1997. Survival Analysis. Springer-Verlag. New York.
Piantadosi, S.. 2005. Clinical Trials, A Methodologic Perspective, 2nd Ed. John Wiley & Sons, Inc. New Jersey.
Devroye, Luc. 1986. Non-Uniform Random Variate Generation. Springer-Verlag. New York.
Matsumoto, M. and Nishimura,T. 1998. 'Mersenne twister: A 623-dimensionally equidistributed uniform pseudorandom number generator.' ACM Trans. On Modeling and Computer Simulations.
Jennison, C., Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman & Hall. Boca Raton, FL.

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

Example 2 – Power for One-Sided Test with Futility Boundaries

Suppose researchers would like to compare two treatments with a one-sided test at each look. Further, suppose they would like to terminate the study early when it can be deemed highly unlikely that the new treatment is better than the standard. Suppose the control group hazard rate is 1.49. The researchers wish to know the power of the test if the treatment group hazard rate is 1.0. The sample size at the final look is to be 200 per group. Testing will be done at the 0.025 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 for both significance and futility boundaries.

Find the power and test boundaries assuming equal sample sizes per arm and one-sided hypothesis tests.

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 1 Tab

Solve For	**Power**
Test Type	**Logrank**
Alternative Hypothesis	**H1: Hazard1 > Hazard2**
Simulations	**10000**
Random Seed	**3856152** (for Reproducibility)
Alpha	**0.025**
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**200**
Percent in Group 1	**50**
Input Type	**Hazard Rate**
h1 (Hazard Rate of Control Group)	**1.49**
Treatment Group Parameter	**h2 (Hazard Rate)**
h2 (Hazard Rate of Treatment Group)	**1.0**

Design 2 Tab

Controls Lost	**0**
Treatments Lost	**0**
For Treatments Lost under H0, use	**Controls Lost**
Noncompliance Proportion (Control)	**0**
NCh1 (Noncompliance Hazard, Control)	**1.0**
At time of noncompliance, start NCh1 at	**Current time**
Noncompliance Proportion (Treatment)	**0**
NCh2 (Noncompliance Hazard, Treatment)	**1.0**
At time of noncompliance, start NCh2 at	**Current time**
For Treatment Noncomp. under H0, use	**Control Noncompliance**

Accrual Time (Integers Only) **0**
Accrual Pattern ..... **Equal (Uniform)**
Total Time (Integers Only) **5**

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 Hazard 1 = Hazard 2.

Solve For:	Power
Hypotheses:	H0: Hazard1 = Hazard2; H1: Hazard1 > Hazard2
Test Statistic:	Logrank Test
Alpha-Spending Function:	O'Brien-Fleming Analog
Beta-Spending Function:	O'Brien-Fleming Analog
Futility Boundary Type:	Non-Binding
Number of Looks:	5
Simulations:	10000
Pool Size:	20000
Random Seed:	3856152 (User-Entered)

Numeric Summary for Scenario 1

Power			Alpha				
Value	**95% LCL**	**95% UCL**	**Target**	**Actual**	**95% LCL**	**95% UCL**	**Beta**
0.786	0.778	0.794	0.025	0.025	0.022	0.028	0.214

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.671	1.49	1	0	Equal	5

		Noncompliance			
Loss1	**Loss2**	**Prop 1**	**h1**	**Prop 2**	**h2**
0	0	0	1	0	1

Whole Study Averages

Study Length		Cum. Subject Time			
		H0		H1	
H0	H1	G1	G2	G1	G2
1.8	3.3	59.3	59.3	65.3	93.2

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100	100	100	100	88.4	88.4	97.4	93.2

Detailed Input

Time Period	Accrual Pattern	Control Hazard Rate h1	Trt Hazard Rate h2	Control Loss Ls1	Trt Loss Ls2	NComp Prop Control NCP1	NComp Hazard Control NCh1	NComp Prop Trt NCP2	NComp Hazard Trt NCh2
1	100% Accrual	1.49	1	0	0	0	1	0	1
2	100% Accrual	1.49	1	0	0	0	1	0	1
3	100% Accrual	1.49	1	0	0	0	1	0	1
4	100% Accrual	1.49	1	0	0	0	1	0	1
5	100% Accrual	1.49	1	0	0	0	1	0	1

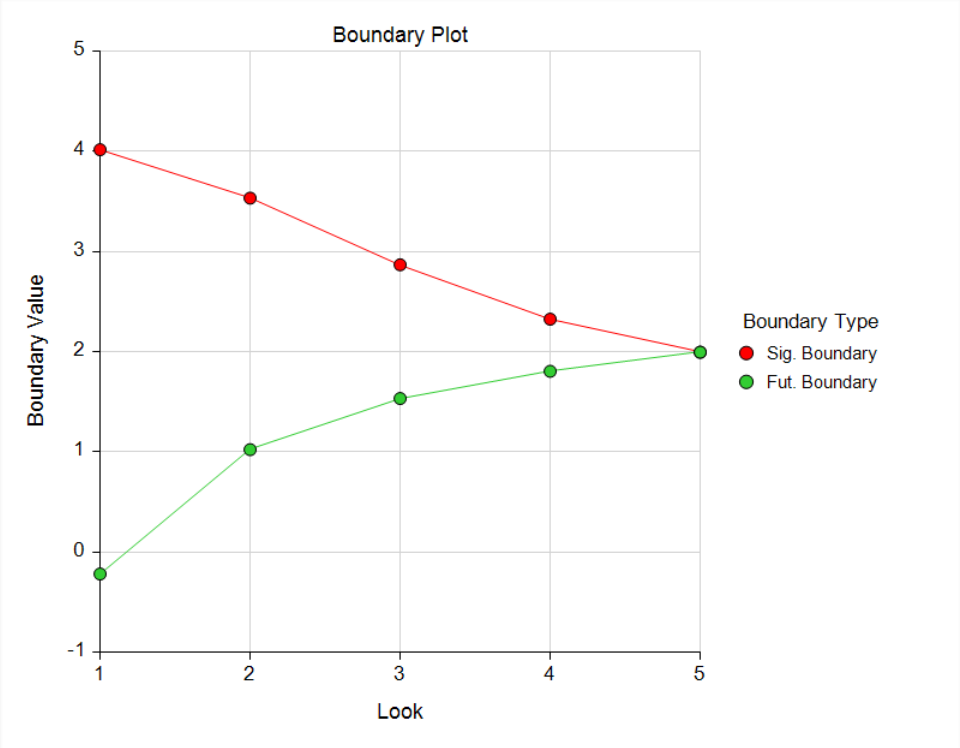
Look Details for Scenario 1

		Sample Size		Events				Cum. Subject Time	
Look	Time	Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	1	100	100	77.5	77.5	63.2	63.2	52.0	63.2
2	2	100	100	94.9	94.9	86.4	86.4	63.7	86.5
3	3	100	100	98.8	98.8	95.0	95.0	66.3	95.0
4	4	100	100	99.7	99.7	98.2	98.2	66.9	98.2
5	5	100	100	99.9	99.9	99.3	99.3	67.1	99.3

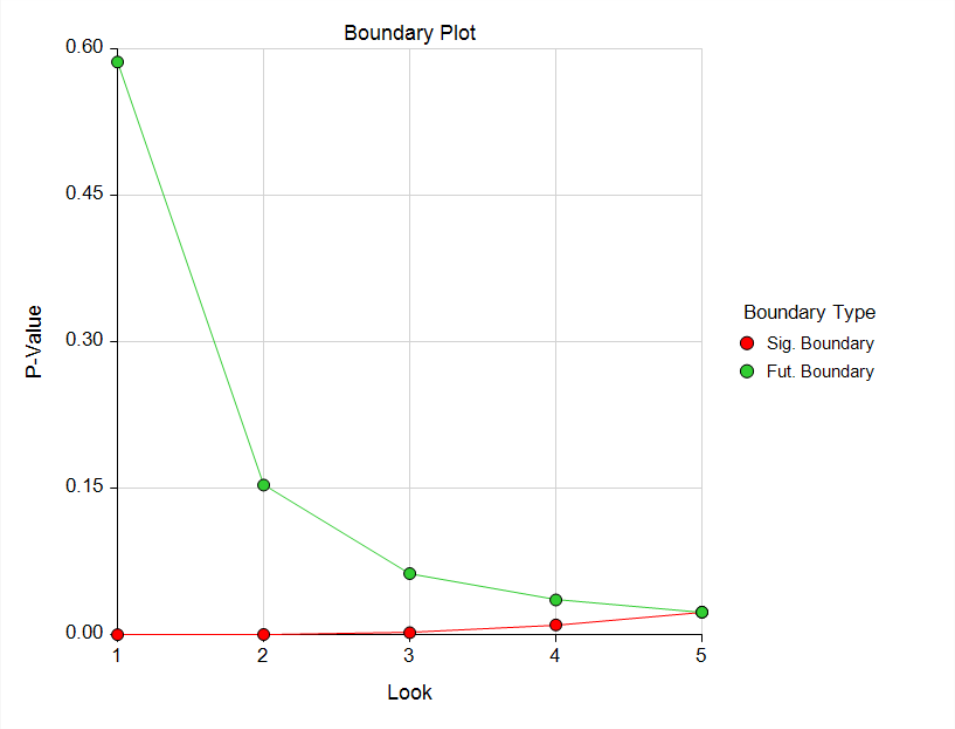
Boundaries for Scenario 1

	Significance Boundary		Futility Boundary	
Look	Z-Value Scale	P-Value Scale	Z-Value Scale	P-Value Scale
1	4.017	0.000	-0.219	0.587
2	3.534	0.000	1.023	0.153
3	2.868	0.002	1.533	0.063
4	2.325	0.010	1.804	0.036
5	1.995	0.023	1.995	0.023

Boundary Plot



Boundary Plot - P-Value



Significance Boundaries with 95% Simulation Confidence Intervals for Scenario 1

	Z-Value Boundary			P-Value Boundary		
Look	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	4.017			0.000		
2	3.534	3.417	4.278	0.000	0.000	0.000
3	2.868	2.766	3.001	0.002	0.001	0.003
4	2.325	2.264	2.381	0.010	0.009	0.012
5	1.995	1.975	2.044	0.023	0.020	0.024

Futility Boundaries with 95% Simulation Confidence Intervals for Scenario 1

	Z-Value Boundary			P-Value Boundary		
Look	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	-0.219	-0.313	-0.143	0.587		
2	1.023	0.977	1.057	0.153	0.145	0.164
3	1.533	1.510	1.554	0.063	0.060	0.066
4	1.804	1.787	1.822	0.036	0.034	0.037
5	1.995	1.985	2.005	0.023	0.022	0.024

Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

	Signif. Boundary		Target		Actual			
Look	Z-Value Scale	P-Value Scale	Spending Function Alpha	Cum. Spending Function Alpha	Alpha Spent	Cum. Alpha Spent	Proportion H0 Sims Outside Futility Boundary	Cum. H0 Sims Outside Futility Boundary
1	4.017	0.000	0.000	0.000	0.000	0.000	0.413	0.413
2	3.534	0.000	0.000	0.000	0.000	0.000	0.427	0.840
3	2.868	0.002	0.003	0.004	0.003	0.004	0.094	0.934
4	2.325	0.010	0.008	0.012	0.008	0.012	0.027	0.960
5	1.995	0.023	0.013	0.025	0.013	0.025	0.015	0.975

Beta-Spending and Alternative Hypothesis Simulation Details for Scenario 1

	Futility Boundary		Target		Actual			
Look	Z-Value Scale	P-Value Scale	Spending Function Beta	Cum. Spending Function Beta	Beta Spent	Cum. Beta Spent	Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
1	-0.219	0.587	0.005	0.005	0.006	0.006	0.048	0.048
2	1.023	0.153	0.044	0.049	0.044	0.050	0.149	0.197
3	1.533	0.063	0.059	0.109	0.059	0.109	0.264	0.461
4	1.804	0.036	0.056	0.165	0.056	0.165	0.216	0.677
5	1.995	0.023	0.049	0.214	0.049	0.214	0.109	0.786

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 1 Tab	
Solve For	**Alpha and Power (Enter Boundaries)**
Test Type	**Logrank**
Alternative Hypothesis	**H1: Hazard1 > Hazard2**
Simulations	**10000**
Random Seed	**3883784** (for Reproducibility)
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**200**
Percent in Group 1	**50**
Input Type	**Hazard Rate**
h1 (Hazard Rate of Control Group)	**1.49**
Treatment Group Parameter	**h2 (Hazard Rate)**
h2 (Hazard Rate of Treatment Group)	**1.0**

Design 2 Tab	
Controls Lost	**0**
Treatments Lost	**0**
For Treatments Lost under H0, use	**Controls Lost**
Noncompliance Proportion (Control)	**0**
NCh1 (Noncompliance Hazard, Control)	**1.0**
At time of noncompliance, start NCh1 at	**Current time**
Noncompliance Proportion (Treatment)	**0**
NCh2 (Noncompliance Hazard, Treatment)	**1.0**
At time of noncompliance, start NCh2 at	**Current time**
For Treatment Noncomp. under H0, use	**Control Noncompliance**
Accrual Time (Integers Only)	**0**
Accrual Pattern	**Equal (Uniform)**
Total Time (Integers Only)	**5**

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 Hazard 1 = Hazard 2.

Solve For:	Alpha and Power (Enter Boundaries)
Hypotheses:	H0: Hazard1 = Hazard2; H1: Hazard1 > Hazard2
Test Statistic:	Logrank Test
Type of Boundaries:	Significance and Futility Boundaries
Number of Looks:	5
Simulations:	10000
Pool Size:	20000
Random Seed:	3883784 (User-Entered)

Numeric Summary for Scenario 1

Power			Alpha			
Value	95% LCL	95% UCL	Value	95% LCL	95% LCL	Beta
0.966	0.963	0.97	0.161	0.154	0.168	0.034

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.671	1.49	1	0	Equal	5

		Noncompliance			
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0	0	0	1	0	1

Whole Study Averages

Study Length		Cum. Subject Time			
		H0		H1	
H0	H1	G1	G2	G1	G2
3.8	3.1	65.9	66	62.5	87.4

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100	100	100	100	98.4	98.4	93.1	87.3

Detailed Input

Time Period	Accrual Pattern	Control Hazard Rate h1	Trt Hazard Rate h2	Control Loss Ls1	Trt Loss Ls2	NComp Prop Control NCP1	NComp Hazard Control NCh1	NComp Prop Trt NCP2	NComp Hazard Trt NCh2
1	100% Accrual	1.49	1	0	0	0	1	0	1
2	100% Accrual	1.49	1	0	0	0	1	0	1
3	100% Accrual	1.49	1	0	0	0	1	0	1
4	100% Accrual	1.49	1	0	0	0	1	0	1
5	100% Accrual	1.49	1	0	0	0	1	0	1

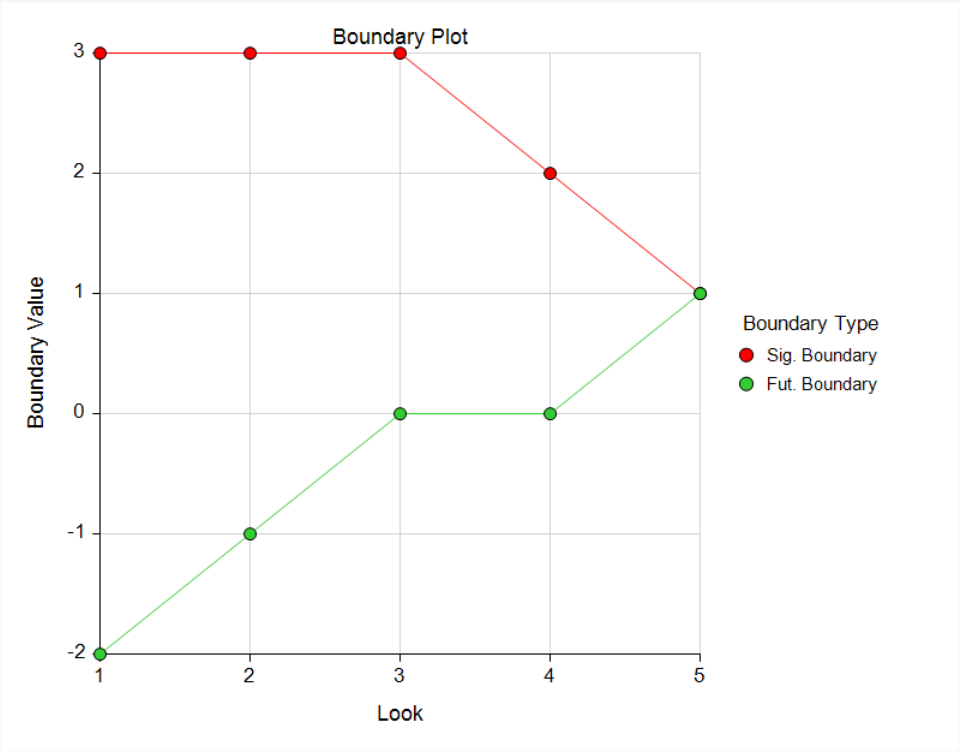
Look Details for Scenario 1

		Sample Size		Events				Cum. Subject Time	
Look	Time	Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	1	100	100	77.4	77.4	63.1	63.1	52.0	63.3
2	2	100	100	94.9	94.9	86.5	86.5	63.7	86.6
3	3	100	100	98.8	98.8	95.0	95.0	66.3	95.1
4	4	100	100	99.7	99.7	98.2	98.2	66.9	98.3
5	5	100	100	99.9	99.9	99.3	99.3	67.0	99.4

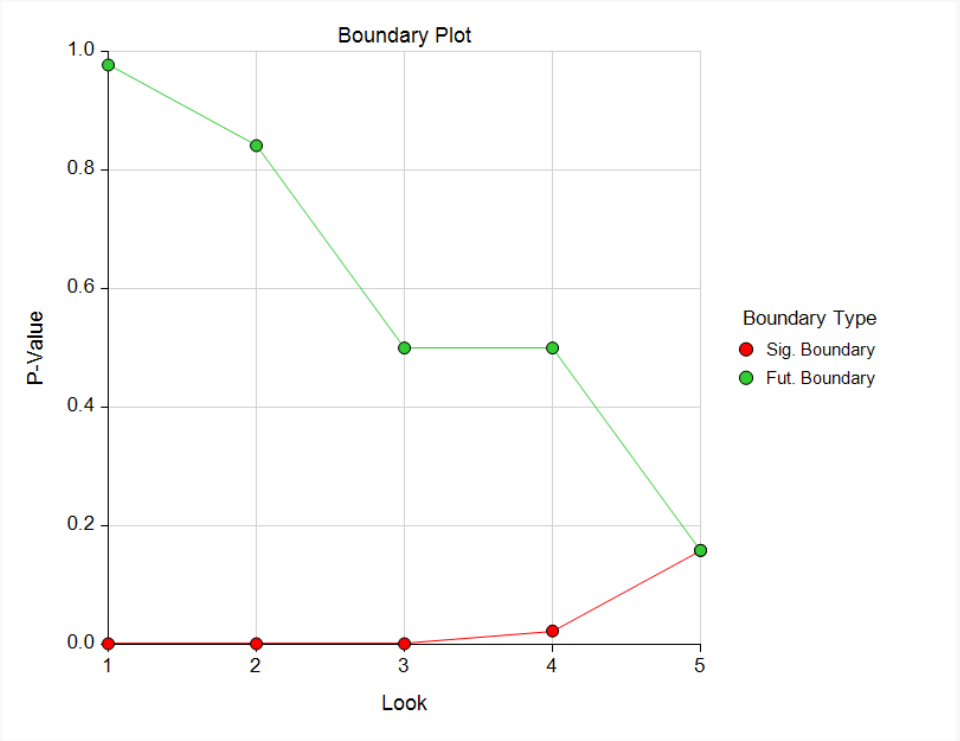
Boundaries for Scenario 1

	Significance Boundary		Futility Boundary	
Look	Z-Value Scale	P-Value Scale	Z-Value Scale	P-Value Scale
1	3	0.001	-2	0.977
2	3	0.001	-1	0.841
3	3	0.001	0	0.500
4	2	0.023	0	0.500
5	1	0.159	1	0.159

Boundary Plot



Boundary Plot - P-Value



Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

Look	Signif. Boundary Z-Value Scale	Signif. Boundary P-Value Scale	Alpha Spent	Cum. Alpha Spent	Proportion H0 Sims Outside Futility Boundary	Cum. H0 Sims Outside Futility Boundary
1	3	0.001	0.001	0.001	0.022	0.022
2	3	0.001	0.001	0.002	0.137	0.159
3	3	0.001	0.000	0.002	0.338	0.497
4	2	0.023	0.020	0.022	0.009	0.506
5	1	0.159	0.139	0.161	0.333	0.839

Beta-Spending and Alternative Hypothesis Simulation Details for Scenario 1

Look	Futility Boundary Z-Value Scale	Futility Boundary P-Value Scale	Beta Spent	Cum. Beta Spent	Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
1	-2	0.977	0.000	0.000	0.265	0.265
2	-1	0.841	0.000	0.000	0.142	0.407
3	0	0.500	0.003	0.004	0.041	0.449
4	0	0.500	0.000	0.004	0.342	0.791
5	1	0.159	0.030	0.034	0.176	0.966

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 1, we examine the power and alpha generated by the set of two-sided significance boundaries (+/- 4.101, +/- 3.290, +/- 2.644, +/- 2.245, +/- 1.982).

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 1 Tab

Solve For	**Alpha and Power (Enter Boundaries)**
Test Type	**Logrank**
Alternative Hypothesis	**H1: Hazard1 ≠ Hazard2**
Simulations	**10000**
Random Seed	**15199887** (for Reproducibility)
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**200**
Percent in Group 1	**50**
Input Type	**Hazard Rate**
h1 (Hazard Rate of Control Group)	**1.4**
Treatment Group Parameter	**h2 (Hazard Rate)**
h2 (Hazard Rate of Treatment Group)	**1.0**

Design 2 Tab

Controls Lost	**0**
Treatments Lost	**0**
For Treatments Lost under H0, use	**Controls Lost**
Noncompliance Proportion (Control)	**0**
NCh1 (Noncompliance Hazard, Control)	**1.0**
At time of noncompliance, start NCh1 at	**Current time**
Noncompliance Proportion (Treatment)	**0**
NCh2 (Noncompliance Hazard, Treatment)	**1.0**
At time of noncompliance, start NCh2 at	**Current time**
For Treatment Noncomp. under H0, use	**Control Noncompliance**
Accrual Time (Integers Only)	**0**
Accrual Pattern	**Equal (Uniform)**
Total Time (Integers Only)	**5**

Looks & Boundaries Tab

Number of Looks	**5**
Equally Spaced	**Checked**
Significance Boundary	**4.101, 3.290, 2.644, 2.245, 1.982** (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 Hazard 1 = Hazard 2.

Solve For:	Alpha and Power (Enter Boundaries)
Hypotheses:	H0: Hazard1 = Hazard2; H1: Hazard1 ≠ Hazard2
Test Statistic:	Logrank Test
Type of Boundaries:	Significance Boundaries Only
Number of Looks:	5
Simulations:	10000
Pool Size:	20000
Random Seed:	15199887 (User-Entered)

Numeric Summary for Scenario 1

Power			Alpha			
Value	95% LCL	95% UCL	Value	95% LCL	95% LCL	Beta
0.644	0.635	0.653	0.049	0.045	0.053	0.356

N1	N2	HR	h1	h2	Accrual Time	Accrual Pattern	Total Time
100	100	0.714	1.4	1	0	Equal	5

		Noncompliance			
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0	0	0	1	0	1

Whole Study Averages

Study Length		Cum. Subject Time			
		H0		H1	
H0	H1	G1	G2	G1	G2
5	3.9	71.2	71.4	70.1	95.8

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
100	100	100	100	99.9	99.9	98.3	95.7

The values obtained from any given run of this example will vary slightly due to the variation in simulations. The power and alpha generated with these boundaries are very close to the values of Example 1.

Example 5 – Validation Using Lakatos (2002)

Lakatos (2002), page 1983, presents an example of a one-sided complex group sequential survival trial. The total time of the trial is 5 years, and the setup is specified in terms of months. The accrual period is two years, but the accrual pattern varies according to month. The noncompliance pattern changes after the first year from 5% to 10%. Survival is represented in terms of mortality and varies across time. The treatment group mortality is 0.775 times the yearly control group mortality. With alpha equal to 0.025 and a sample size of 1244, the power for 10 looks with O'Brien-Fleming boundaries is 0.90. The O'Brien-Fleming alpha values are input directly in this example since they differ slightly from the O'Brien-Fleming analog values. All yearly rates in this example are converted to monthly rates for consistency.

Warning: the time to run this example is around 10 to 15 hours at current computer speeds.

Accrual Percent: months 1 to 3 (10), months 4 to 6 (20), months 7 to 9 (40), months 10 to 12 (60), months 13 to 15 (80), months 16 to 24 (100).

Noncompliance Control: 0.00427 / month

Noncompliance Treatment: months 1 to 12 (0.00874 / month), months 13 to 60 (0.00427 / month)

Mortality Control: months 1 to 3 (0.0403 / month), months 4 to 6 (0.0248 / month), months 7 to 12 (0.0237 / month), months 13 to 24 (0.0215 / month), months 25 to 60 (0.0184 / month).

Mortality Treatment: months 1 to 3 (0.0295 / month), months 4 to 6 (0.0186 / month), months 7 to 12 (0.0178 / month), months 13 to 24 (0.0162 / month), months 25 to 60 (0.0139 / month).

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 5** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design 1 Tab

Solve For	**Power**
Test Type	**Logrank**
Alternative Hypothesis	**H1: Hazard1 > Hazard2**
Simulations	**200000**
Random Seed	**5644887** (for Reproducibility)
Alpha	**0.025**
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**1244**
Percent in Group 1	**50**
Input Type	**Mortality**
M1 (Mortality of Control Group)	**=pC**
Treatment Group Parameter	**M2 (Mortality)**
M2 (Mortality of Treatment Group)	**=pE**
T0 (Mortality Time)	**1.0**

Design 2 Tab

Controls Lost	**0**
Treatments Lost	**0**
For Treatments Lost under H0, use	**Controls Lost**
Noncompliance Proportion (Control)	**=dropin**
NCM1 (Noncompliance Mortality, Control)	**M2**
At time of noncompliance, start NCM1 at	**Current time**
Noncompliance Proportion (Treatment)	**=NonComp**
NCM2 (Noncompliance Mortality, Treatment)	**M1**
At time of noncompliance, start NCM2 at	**Current time**
For Treatment Noncomp. under H0, use	**Control Noncompliance**
Accrual Time (Integers Only)	**24**
Accrual Pattern	**Non-Uniform (Spreadsheet Entry)**
Accrual Values in Columns	**=Accrual**
Total Time (Integers Only)	**60**

Looks & Boundaries Tab

Specification of Looks and Boundaries	**Custom**
Number of Looks	**10**
Equally Spaced	**Checked**
Type of Futility Boundary	**None**
Percent of Alpha Spent	**0, 0, 0, 0.00036, 0.00248, 0.00415, 0.00474, 0.00465, 0.00442, 0.00420**

Input Spreadsheet Data

Row	Accrual	NonComp	dropin	pC	pE
1	10	0.0087416109547	0.00427	0.04035	0.029545927
2	10	0.0087416109547	0.00427	0.04035	0.029545927
3	10	0.0087416109547	0.00427	0.04035	0.029545927
4	20	0.0087416109547	0.00427	0.02478	0.018576970
5	20	0.0087416109547	0.00427	0.02478	0.018576970
6	20	0.0087416109547	0.00427	0.02478	0.018576970
7	40	0.0087416109547	0.00427	0.02369	0.017786700
8	40	0.0087416109547	0.00427	0.02369	0.017786700
9	40	0.0087416109547	0.00427	0.02369	0.017786700
10	60	0.0087416109547	0.00427	0.02369	0.017786700
11	60	0.0087416109547	0.00427	0.02369	0.017786700
12	60	0.0087416109547	0.00427	0.02369	0.017786700
13	80	0.0042653187776	0.00427	0.02154	0.016226825
14	80	0.0042653187776	0.00427	0.02154	0.016226825
15	80	0.0042653187776	0.00427	0.02154	0.016226825
16	100	0.0042653187776	0.00427	0.02154	0.016226825
17	100	0.0042653187776	0.00427	0.02154	0.016226825
18	100	0.0042653187776	0.00427	0.02154	0.016226825
19	100	0.0042653187776	0.00427	0.02154	0.016226825
20	100	0.0042653187776	0.00427	0.02154	0.016226825
21	100	0.0042653187776	0.00427	0.02154	0.016226825
22	100	0.0042653187776	0.00427	0.02154	0.016226825
23	100	0.0042653187776	0.00427	0.02154	0.016226825
24	100	0.0042653187776	0.00427	0.02154	0.016226825
25		0.0042653187776	0.00427	0.01842	0.013936857

26	0.0042653187776	0.00427	0.01842	0.013936857
27	0.0042653187776	0.00427	0.01842	0.013936857
28	0.0042653187776	0.00427	0.01842	0.013936857
29	0.0042653187776	0.00427	0.01842	0.013936857
30	0.0042653187776	0.00427	0.01842	0.013936857
31	0.0042653187776	0.00427	0.01842	0.013936857
32	0.0042653187776	0.00427	0.01842	0.013936857
33	0.0042653187776	0.00427	0.01842	0.013936857
34	0.0042653187776	0.00427	0.01842	0.013936857
35	0.0042653187776	0.00427	0.01842	0.013936857
36	0.0042653187776	0.00427	0.01842	0.013936857
37	0.0042653187776	0.00427	0.01842	0.013936857
38	0.0042653187776	0.00427	0.01842	0.013936857
39	0.0042653187776	0.00427	0.01842	0.013936857
40	0.0042653187776	0.00427	0.01842	0.013936857
41	0.0042653187776	0.00427	0.01842	0.013936857
42	0.0042653187776	0.00427	0.01842	0.013936857
43	0.0042653187776	0.00427	0.01842	0.013936857
44	0.0042653187776	0.00427	0.01842	0.013936857
45	0.0042653187776	0.00427	0.01842	0.013936857
46	0.0042653187776	0.00427	0.01842	0.013936857
47	0.0042653187776	0.00427	0.01842	0.013936857
48	0.0042653187776	0.00427	0.01842	0.013936857
49	0.0042653187776	0.00427	0.01842	0.013936857
50	0.0042653187776	0.00427	0.01842	0.013936857
51	0.0042653187776	0.00427	0.01842	0.013936857
52	0.0042653187776	0.00427	0.01842	0.013936857
53	0.0042653187776	0.00427	0.01842	0.013936857
54	0.0042653187776	0.00427	0.01842	0.013936857
55	0.0042653187776	0.00427	0.01842	0.013936857
56	0.0042653187776	0.00427	0.01842	0.013936857
57	0.0042653187776	0.00427	0.01842	0.013936857
58	0.0042653187776	0.00427	0.01842	0.013936857
59	0.0042653187776	0.00427	0.01842	0.013936857
60	0.0042653187776	0.00427	0.01842	0.013936857

Output

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

Scenario 1 Numeric Results for Group Sequential Testing Hazard 1 = Hazard 2.

Solve For:	Power
Hypotheses:	H0: Hazard1 = Hazard2; H1: Hazard1 > Hazard2
Test Statistic:	Logrank Test
Alpha-Spending Function:	Custom
Beta-Spending Function:	None
Futility Boundary Type:	None
Number of Looks:	10
Simulations:	100
Pool Size:	10000

Numeric Summary for Scenario 1

Power			Alpha				
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
0.8954	0.89405	0.89674	0.025	0.025	0.02432	0.02568	0.10461

N1	N2	MR	M1	M2	Accrual T0	Accrual Time	Total Pattern	Time
622	622	Calc.	pC	pE	1	24	Accrual	60

		Noncompliance			
Loss1	Loss2	Prop 1	M1	Prop 2	M2
0	0	dropin	M2	NonComp	M1

Whole Study Averages

Study Length		Cum. Subject Time			
		H0		H1	
H0	H1	G1	G2	G1	G2
59.6	38.1	16555.6	16552.6	9790.7	10591.1

Sample Size				Events			
H0		H1		H0		H1	
G1	G2	G1	G2	G1	G2	G1	G2
622	622	621.1	621.1	381.2	381.3	250.4	206.5

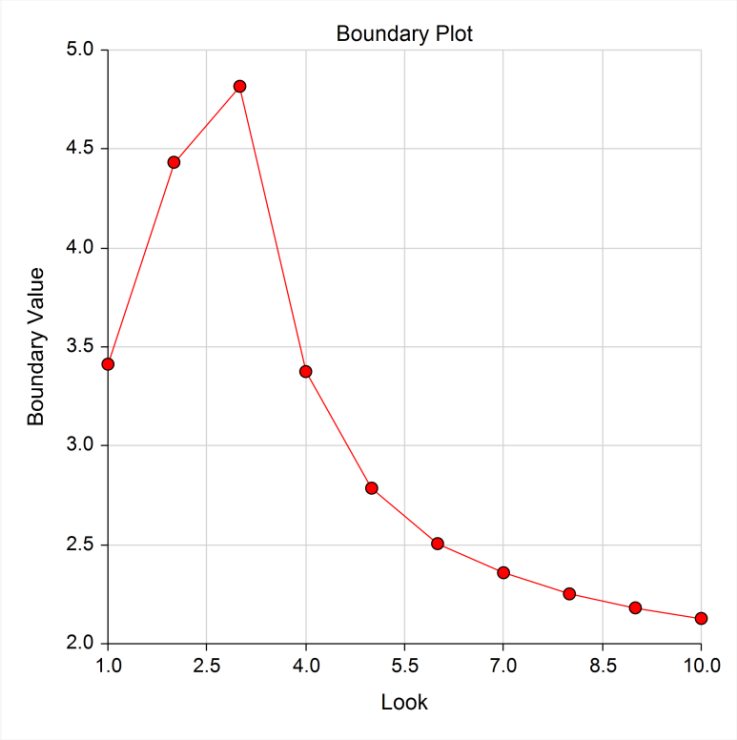
Look Details for Scenario 1

		Sample Size		Events				Cum. Subject Time	
Look	Time	Group 1	Group 2	Group 1	% of S.S.	Group 2	% of S.S.	Group 1	Group 2
1	6	37	37	3.2	8.7	2.4	6.5	84.4	86.0
2	12	159	159	19.9	12.5	15.1	9.5	574.2	590.3
3	18	378	378	61.7	16.3	47.5	12.6	1918.1	1988.0
4	24	622	622	131.3	21.1	102.5	16.5	4351.0	4548.0
5	30	622	622	197.2	31.7	157.3	25.3	7085.2	7492.4
6	36	622	622	248.7	40.0	202.4	32.5	9474.2	10141.5
7	42	622	622	291.0	46.8	241.1	38.8	11583.3	12540.2
8	48	622	622	326.2	52.4	274.4	44.1	13460.5	14723.1
9	54	622	622	356.3	57.3	303.9	48.9	15143.4	16718.8
10	60	622	622	383.2	61.6	331.1	53.2	16655.5	18544.6

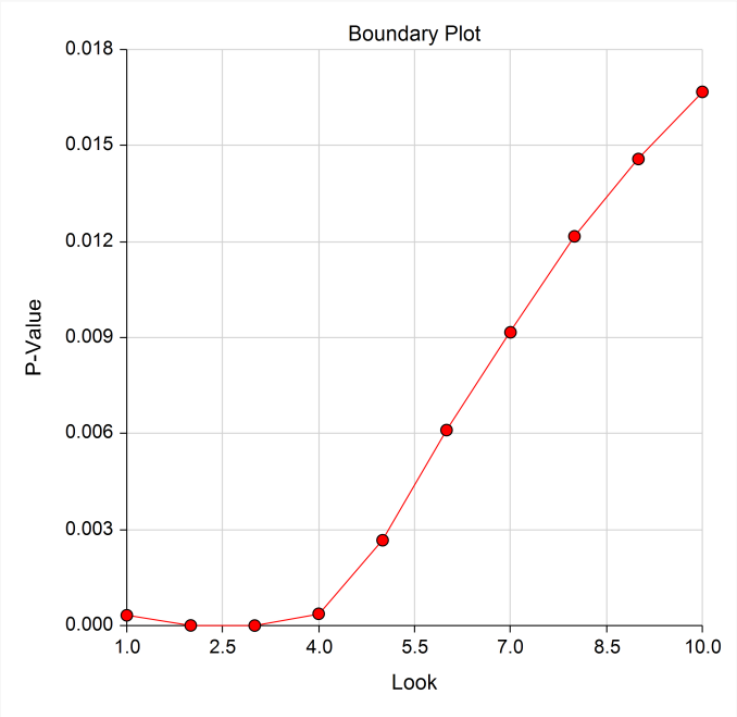
Boundaries for Scenario 1

	Significance Boundary	
Look	Z-Value Scale	P-Value Scale
1	3.68216	0.00012
2	4.31303	0.00001
3	4.19341	0.00001
4	3.35845	0.00039
5	2.74671	0.00301
6	2.50629	0.00610
7	2.36090	0.00912
8	2.25005	0.01222
9	2.18333	0.01451
10	2.12612	0.01675

Boundary Plot



Boundary Plot - P-Value



Significance Boundaries with 95% Simulation Confidence Intervals for Scenario 1

	Z-Value Boundary			P-Value Boundary		
Look	Value	95% LCL	95% UCL	Value	95% LCL	95% UCL
1	3.68216			0.00012		
2	4.31303			0.00001		
3	4.19341			0.00001		
4	3.35845	3.31196	3.43835	0.00039	0.00029	0.00046
5	2.74671	2.72330	2.77454	0.00301	0.00276	0.00323
6	2.50629	2.48458	2.52475	0.00610	0.00579	0.00649
7	2.36090	2.34836	2.37813	0.00912	0.00870	0.00943
8	2.25005	2.23529	2.26678	0.01222	0.01170	0.01270
9	2.18333	2.17056	2.19585	0.01451	0.01405	0.01498
10	2.12612	2.11348	2.13595	0.01675	0.01634	0.01728

Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

	Signif. Boundary		Target		Actual			
Look	Z-Value Scale	P-Value Scale	Spending Function Alpha	Cum. Spending Function Alpha	Alpha Spent	Cum. Alpha Spent	Proportion H1 Sims Outside Signif. Boundary	Cum. H1 Sims Outside Signif. Boundary
1	3.68216	0.00012	0.00000	0.00000	0.00000	0.00000	0.00001	0.00001
2	4.31303	0.00001	0.00000	0.00000	0.00000	0.00000	0.00019	0.00020
3	4.19341	0.00001	0.00000	0.00000	0.00000	0.00000	0.00323	0.00343
4	3.35845	0.00039	0.00036	0.00036	0.00036	0.00036	0.11440	0.11783
5	2.74671	0.00301	0.00248	0.00284	0.00248	0.00284	0.32242	0.44025
6	2.50629	0.00610	0.00415	0.00699	0.00415	0.00699	0.20077	0.64102
7	2.36090	0.00912	0.00474	0.01173	0.00474	0.01173	0.11772	0.75874
8	2.25005	0.01222	0.00465	0.01638	0.00465	0.01638	0.06901	0.82774
9	2.18333	0.01451	0.00442	0.02080	0.00442	0.02080	0.04062	0.86836
10	2.12612	0.01675	0.00420	0.02500	0.00420	0.02500	0.02704	0.89540

The values obtained from any given run of this example will vary slightly due to the variation in simulations. The power generated for this example is 0.8954, very close to the value in Lakatos (2008), although 0.90 is not in the simulation confidence interval. Also, the first two boundary values are not as extreme as they should be because there were not enough simulations to obtain extreme boundary values. The first three boundary values in Lakatos (2002) were set to 5.0.